E.C. 6/88

PRACTICE OF MEDICINE

VOLUME III

PRACTICE OF MEDICINE

EDITED BY

FREDERICK TICE, M.D.

PROFESSOR OF MEDICINE AND CLINICAL MEDICINE, AND
HEAD OF THE DEPARTMENT OF MEDICINE,
UNIVERSITY OF ILLINOIS, COLLEGE
OF MEDICINE

FOREWORD BY

M. W. IRELAND, M.D.

SURGEON-GENERAL, U. S. ARMY

VOLUME III

HAGERSTOWN, MARYLAND
. F. PRIOR COMPANY, INC.
1924

Printed in the United States of America

CONTENTS

VOLUME III

SECTION II: INFECTIOUS DISEASES (*Continued*)

CHAPTER PAGE

V. ACUTE LOBAR PNEUMONIA 1

By Charles R. Austrian

Synonyms 1
Definition 2
Etiology 2
  Predisposing Causes 2
  Exciting Cause: the Organism 5
Symptomatology 15
  General Course of a Typical Case 15
  Clinical History 16
  Physical Findings 25
  Laboratory Findings 29
Diagnosis 35
  X-ray Examination 38
Complications 39
  Respiratory System 39
  Cardiovascular System 43
  Urinary System 46
  Genital System 46
  Skin 46
  Nervous System 46
  Organs of Special Sense 48
  Muscular System 48
  Gastro-intestinal System 48
Pneumonia in Association with Other Diseases 50
  Infectious Diseases 50
  Non-infectious Diseases 52
Clinical Varieties—Types 52
  Central Pneumonia 52
  Massive Pneumonia 53
  Apical Pneumonia 53
  Migratory Pneumonia 53
  Short Term, or Abortive, Pneumonia 53
  Senile, or Asthenic, Pneumonia 53
  Terminal, or Terminating, Pneumonia 54
  Pneumonia in Infancy and Childhood 54
  Postoperative Pneumonia 55
  Pneumonia in Pregnancy 56
  Traumatic Pneumonia 56
  Pneumonia Following Immersion in Water 56
  Typhoid Pneumonia 56
  Secondary Pneumonia 57
  Organizing Pneumonia 57
Treatment 57

CHAPTER PAGE
Prophylaxis 57
General Management 59
Treatment of Symptoms 62
Specific Treatment 66
Prognosis 70
Influencing Factors 70
Modes of Death 72
Duration 73
Termination 73
Relapse 73
Pathology 73
Historical Summary 76
Distribution of the Changes in the Lungs 76
Lesions in Other Organs 76

VI. CEREBROSPINAL FEVER 83
By J. P. Leake
Definition 83
Etiology 84
Epidemiology 84
Bacteriology 87
Symptomatology 90
Clinical History 90
Physical Findings 92
Special and Laboratory Findings 97
Differential Diagnosis 103
Complications and Sequelæ 105
Clinical Types 106
Meningitis in Early Infancy 106
Ordinary Acute Cases 108
Subacute and Chronic Types 109
Hyperacute and Fulminating Types 109
Treatment 110
Prophylaxis 110
General Management 112
Symptomatic Treatment 112
Serum Treatment 113
Surgical Indications 115
Treatment of Complications and Sequelæ 116
Convalescence 117
Prognosis 117
As to Recovery 117
As to Function 118
Pathological Anatomy 118
Historical Summary 119

VII. DIPHTHERIA 131
By Samuel Sidney Woody
Definition 131
Etiology 131
Predisposing Causes 131
Exciting Cause: the Organism 132
Symptomatology 135
Clinical History 135
Second Attacks 137
Diagnosis 137
Differential Diagnosis 139
Complications and Sequelæ 144

CHAPTER PAGE
Association with Other Diseases 148
Clinical Varieties 149
Treatment 153
  Prophylaxis 153
  General Management 158
  Medicinal Treatment 159
  Local Treatment 160
  Surgical Treatment 160
  Treatment of complications 163
  Management of Convalescence 164
Prognosis 165
Pathology 165
Historical Summary 169

VIII. ERYSIPELAS 177

By H. B. Cushing

Definition 177
Etiology 177
  Predisposing Causes 177
  Exciting Cause 178
Symptomatology 178
  Clinical History 178
  Physical Findings 178
Diagnosis 179
Complications and Sequelæ 180
Association with Other Diseases 181
Clinical Varieties 181
  Migratory Erysipelas 181
  Surgical Erysipelas 181
  Recurrent Erysipelas 182
  Erysipelas of the Navel 182
  Afebrile Erysipelas 182
  Cellulocutaneous Erysipelas 182
Treatment 182
  Prophylaxis 182
  General Management 182
  Local Treatment 183
  Specific Therapy 183
Prognosis 184
Pathology 184
Historical Summary 185

IX. VARIOLA (Small-pox) 187

By Samuel Sidney Woody

Definition 187
Etiology 187
  Predisposing Causes 187
  Exciting Cause: the Organism 188
Symptomatology 189
  Clinical History 189
Diagnosis 193
Complications 197
Clinical Varieties 197
  Variola Hemorrhagica 198
  Variola Vera 198
  Varioloid 199

CHAPTER PAGE
Variola Sine Exanthem 200
Treatment 200
Prophylaxis 200
General Treatment 202
Serum Therapy 206
Prognosis 207
Pathology 207
Historical Summary 209

X. VACCINIA (VACCINATION) 215
By Samuel Sidney Woody
Definition 215
Relation of Vaccinia to Variola 215
Symptomatology 215
Mode of Onset and Normal Course 215
Indications for Vaccination 217
Technic of Vaccination 217
Revaccination 218
Complications and Association with Other Diseases . . . 218
Treatment 219
Historical Summary 219

XI. VARICELLA (CHICKEN-POX) 223
By Samuel Sidney Woody
Definition 223
Etiology 223
Symptomatology 224
Prodromal Symptoms—Clinical History 224
Diagnosis 225
Complications 226
Sequelæ 227
Association with Other Diseases 227
Clinical Varieties 228
Treatment 228
Prophylaxis 228
General Management 229
Management of Convalescence 230
Prognosis 230
Pathology 230
Historical Summary 231

XII. SCARLET FEVER 233
By Samuel Sidney Woody
Definition 233
Predisposing Causes 233
Exciting Cause 235
Symptomatology 239
Clinical History 239
Laboratory Findings 243
Diagnosis 243
Complications and Sequelæ 246
Relapses, Recurrences and Second Attacks of Scarlet Fever 250
Association with Other Diseases 251
Clinical Varieties 252
Scarlatina Simplex 252
Scarlatina Anginosa 253

CHAPTER PAGE
Scarlatina Maligna 254
Surgical Scarlatina—Puerperal Scarlatina 254
Scarlatina Sine Exanthem 254
Treatment 255
Prophylaxis 255
General Management 260
Serum Therapy 270
Prognosis 271
Pathology 272
Circulatory System 273
Respiratory System 273
Digestive System 274
Urinary System 274
Endocrine Glands 275
Osseous and Nervous Systems 276
Blood 276
Skin 276
Historical Summary 277

XIII. RUBEOLA (MEASLES) 281

By WILLIAM A. JENKINS

Definition 281
Etiology 281
Predisposing Causes 281
Exciting Causes 282
Symptomatology 283
Incubation 283
Invasion 284
Eruption 286
Desquamation 288
Laboratory Findings 288
Diagnosis 288
Association with Other Diseases 289
Complications 289
The Skin 289
The Eye 289
The Nose 289
The Ear 289
The Air-passages 290
The Gastro-intestinal Tract 290
The Kidneys 290
The Heart 290
The Nervous System 290
Sequelæ 290
The Air-passages 290
The Ear 291
The Kidneys 291
Treatment 291
Prophylaxis 291
Curative Treatment 292
Prognosis 298
Pathology 299
History 300

XIV. RUBELLA (GERMAN MEASLES) 301

By WILLIAM A. JENKINS

Definition 301
Etiology 301

CHAPTER PAGE

- Symptomatology . . . 301
  - Incubation . . . 301
  - Invasional or Prodromal Stage . . . 302
  - Eruption . . . 303
  - Desquamation . . . 305
- Diagnosis . . . 305
- Complications and Sequelæ . . . 306
- Treatment . . . 307
  - Prophylaxis . . . 307
  - Curative Treatment . . . 308
- Prognosis . . . 308
- Pathology . . . 309
- History . . . 309

XV. PAROTITIS EPIDEMICA (MUMPS) . . . 311

BY WILLIAM A. JENKINS

- Definition . . . 311
- Etiology . . . 311
  - Predisposing Causes . . . 311
  - Exciting Causes . . . 312
- Symptomatology . . . 312
  - Period of Incubation . . . 312
  - Invasion . . . 313
  - Anomalies or Irregular Types of Mumps . . . 314
  - Consideration of Special Symptoms . . . 315
  - Laboratory Findings . . . 317
- Diagnosis . . . 317
- Complications . . . 318
  - In the Male . . . 318
  - In the Female Sex . . . 319
  - General Complications . . . 319
- Sequelæ . . . 321
  - Sequelæ of the Genital Tract . . . 321
  - General Sequelæ . . . 321
- Treatment . . . 322
  - Prophylaxis . . . 322
  - Curative Treatment . . . 323
  - Convalescence . . . 326
- Prognosis . . . 326
- Pathology . . . 326
- History . . . 3[illegible]

XVI. SYPHILIS . . . 329

BY VICTOR D. LESPINASSE

- Acquired Syphilis . . . 329
  - Etiology . . . 329
    - Bacteriology of Treponema Pallidum (*Spirochæta Pallida*) 329
  - Symptomatology . . . 332
    - A. Primary Stage . . . 332
    - B. Secondary Stage . . . 336
    - C. Tertiary Stage . . . 344
    - Laboratory Findings . . . 355
    - Special Examinations . . . 365
  - Diagnosis . . . 368
    - A. Diagnosis in Primary Stage . . . 368
    - B. Diagnosis in Secondary Stage . . . 370
    - C. Diagnosis in Tertiary Stage . . . 372

CHAPTER PAGE
D. Diagnosis in Latent Syphilis 374
Differential Diagnosis 375
Clinical Varieties 380
Treatment 381
Prophylaxis 381
General Management 382
Hydrotherapy 385
Constitutional Treatment 386
Plan of Treatment of Syphilis 409
Prognosis 416
Pathology 417
Primary Stage 418
Secondary Stage 418
Tertiary Stage 419
Circulatory System 419
Lymphatic System 420
Respiratory System 420
Digestive System 421
Urinary System 423
Reproductive System 424
Nervous System 425
Muscular System 426
Bones and Joints 426
Endocrine System 428
Blood 429
Skin 429
Organs of Special Sense 429
Hereditary Syphilis 429
Transmission 429
Factors Which Determine the Development of Hereditary Syphilis 430
Characteristic Symptoms of Hereditary Syphilis . . . 430
Diagnosis of Early Hereditary Syphilis 437
Diagnosis of Late Hereditary Syphilis 438
Treatment of Hereditary Syphilis 438
Distribution and Historical Summary 441
Appearance of Syphilis in Europe 441
Appearance of Syphilis in the Orient 442
Appearance of Syphilis in America 442
Historical Summary 443
Sociological Aspects of the Disease 444

XVII. GONOCOCCAL INFECTIONS 451
By David Geiringer and Jorge Campuzano

History of Gonorrhea 451
Prevalence of Gonorrhea 452
Duration of Gonorrhea 452
Etiology 453
Bacteriology of Gonorrhea 453
Pathology of Gonococcal Infection 460
Gonorrhea in the Male 462
Symptomatology of Gonorrhea in the Male 463
Diagnosis of Gonorrheal Infection 468
Treatment of Acute Gonococcal Urethritis 476
Treatment of Chronic Gonorrhea in the Male . . . 490
Complications of Gonorrheal Urethritis and Their Treatment 500
Determination of a Cure 512

CHAPTER PAGE
Gonococcal Infection in the Female 513
  Occurrence 514
  Organs Invaded 514
  Symptoms and Clinical Course 514
  Diagnosis of Gonorrhea in Women 515
  Treatment of Gonococcus Infection in Women 515
  Determination of a Cure 516
Gonorrheal Vulvovaginitis in Children 517
  Etiology 517
  Pathology 517
  Symptoms 517
  Diagnosis 517
  Treatment of Vulvovaginitis in Children 518

XVIII. RABIES 521

By Eugene R. Whitmore

Definition 521
Synonyms 521
Etiology 521
Epidemiology 524
Mechanism of the Disease Process 525
Symptomatology 526
  A. Rabies in the Lower Animals 526
  B. Rabies in Man 528
Diagnosis 530
  Clinical Diagnosis of Rabies in Dogs 530
  Laboratory Diagnosis of Rabies in Dogs 531
  Diagnosis of Rabies in Man 534
Treatment 534
  General Prophylaxis 534
  Personal Prophylaxis 535
  Prophylactic Treatment 535
  Treatment of the Developed Attack of Rabies 544
Prognosis 545
Pathology 545
History 547
Geographical Distribution 548

XIX. MALARIA 551

By Charles C. Bass

Etiology 551
  Predisposing Causes 551
  Exciting Cause 564
Symptomatology 584
  Clinical History 584
  Physical Findings 594
  Laboratory Findings 597
  Special Examinations 602
Diagnosis 602
  Clinical History 602
  Physical Findings 604
  Laboratory Findings 604
Complications and Association with Other Diseases . . . 606
Sequelæ 607
Clinical Varieties 610
  Malaria Infection Without Recognizable Evidence of Its Presence 610

PAGE
Chills; Chills and Fever 610
Intermittent Malarial Fever 611
Remittent Fever 611
Acute and Chronic Malaria 611
Malaria Relapse 611
Benign and Pernicious Malaria 612
Treatment 612
Prophylaxis 612
General Management 626
Diet 627
Climatology 627
Local Treatment 628
Treatment of Symptoms 628
Specific Therapy (Vaccines and Serums) 628
Medicinal Treatment: Drugs 628
Surgical Indications 632
Management of Convalescence 633
Prognosis 633
As to Recovery 633
As to Function 637
Pathology 637
Findings at Autopsy 638
Historical Summary 641
Geographical Distribution 642
Sociological Aspect of Malaria 642
Malaria as a Community Disease 642

INDEX 649

LIST OF ILLUSTRATIONS

VOLUME III

SECTION II. INFECTIOUS DISEASES (*Continued*)

CHAPTER XVII

FIGURE PAGE

GONOCOCCAL INFECTIONS

1. Direct-view irrigating urethroscope for diagnosis and treatment . . 474
2. Janet-Frank syringe 482
3. Chetwood's irrigating nozzle 482
4. Kiefer's irrigating nozzle 482
5. Ultzmann's instillation syringe 483
6. Guyon instillation syringe 483
7. Oberländer's anteroposterior urethral dilator 492
8. Kollmann's urethral dilator; type used for dilating the anterior urethra 492
9. Kollmann's urethral dilator, anteroposterior dilating blades . . . 493
10. Kollmann's urethral dilator, blades for dilating posterior urethra or prostate 493

CHAPTER XVIII

RABIES

1. Rabies tubercle in the medulla 546

CHAPTER XIX

MALARIA

1. Chart showing malaria mortality by months 552
2. Relative prevalence of malaria in Arkansas, by months, as indicated by the number of cases reported 553
3. Blood index by years, to 20 years; first examination 31,459 persons 554
4. Blood index by age-groups; first examination 31,459 persons . . 555
5. Chart showing the percentage of all the malaria found in the first blood examination of 31,459 persons, in each five year age-group 556
6. Apparatus used in cultivation of malaria parasites 574
7. Different forms of malaria cultures 575
8. Resting positions of larvæ 582
9. Temperature chart of single tertian infection 588
10. Temperature chart of double tertian infection 589
11. Temperature chart of single quartan infection 590
12. Temperature chart of double quartan infection 591
13. Temperature chart of triple quartan infection 592
14. Temperature chart of tertian estivo-autumnal malaria . . . 593
15. Temperature chart of quotidian estivo-autumnal malaria . . . 594
16. Calls for malaria, 1916 (estimated) and 1917, Hamburg, Arkansas 621

FIGURE PAGE
17. Showing the distribution of malaria as indicated by the intensity of the shading (America) 643
18. Showing the distribution of malaria as indicated by the intensity of the shading (Europe) 644
19. Showing the distribution of malaria as indicated by the intensity of the shading (Asia, Africa) 645

COLORED PLATES

PLATE FACING PAGE
1. Quartan malaria plasmodia (Plasmodium malariæ) 564
2. Tertian malaria plasmodia (Plasmodium vivax) 566
3. Estivo-autumnal malaria plasmodia (Plasmodium falciparum) . . . 568

PRACTICE OF MEDICINE

VOLUME III

SECTION II

INFECTIOUS DISEASES (CONTINUED)

CHAPTER V

ACUTE LOBAR PNEUMONIA

BY CHARLES R. AUSTRIAN, M.D.

Etiology, p. 2—Predisposing causes, p. 2—Exciting cause: the organism, p. 5—Morphology, p. 5—Virulence, p. 7—Toxin formation, p. 7—Isolation of pneumococcus and determination of type, p. 9—Carriers, p. 11—Epidemiology, p. 11—Pathogenesis, p. 13—Immunity, p. 13.
Symptomatology, p. 15—General course of a typical case, p. 15—Clinical history, p. 16—Physical findings, p. 26—Laboratory findings, p. 30.
Diagnosis, p. 35—Differential diagnosis, p. 36—X-ray examination, p. 38.
Complications, p. 39—Association with other diseases, p. 50—Clinical varieties—types, p. 52.
Treatment, p. 57—Prophylaxis, p. 57—General measures, p. 58—Specific measures, p. 59—Vaccination, p. 59—General management, p. 59—Diet, p. 61—Hydrotherapy, p. 61—Aërotherapy, p. 62—Treatment of symptoms, p. 62—Specific treatment, p. 66—Serum therapy, p. 66—Vaccine therapy, p. 68—Chemotherapy, p. 69.
Prognosis, p. 70—Influencing factors, p. 70—Modes of death, p. 72—Duration, p. 73—Termination, p. 73—Relapse, p. 73.
Pathology, p. 73—Stages, p. 73—Distribution of the changes in the lungs, p. 76—Lesions in other organs, p. 76.
Historical summary, p. 76.

Synonyms.—Peripneumony (Hippocrates); Pneumonia (Aretaeus); Peripneumonia vera (Sydenham); Pneumonic fever (Huxham); Pleuropneumonia; Croupous or fibrinous pneumonia; Lobar pneumonia; Pneumonitis; Sthenic pneumonia; Pulmonary fever; Pneumonie lobaire; fluxion de la poitrine; Lungenentzündung; Kroupöse pneumonie.

Definition.—Lobar pneumonia is an acute infectious disease due to the pneumococcus. It is characterized pathologically by an exudative inflammation of the lungs and clinically by distinctive local and general symptoms.

Though clinically an entity, lobar pneumonia may be caused by a number of different microörganisms—a fact of fundamental importance in the prophylaxis and therapy of the disease.

ETIOLOGY

Lobar pneumonia may appear as a sporadic, an endemic or an epidemic disease, and though it is practically ubiquitous, certain main factors seem to govern its occurrence and spread.

Predisposing Causes.—GEOGRAPHICAL DISTRIBUTION.—Pneumonia occurs in all parts of the world, but is most frequent in the temperate zones and in regions with a wide daily range of temperature. It causes more deaths in North America and in Europe than does any other acute infectious disease.

COLD.—Experimentally it has been shown in animals that chilling of the body surface is followed by increased bronchial secretion and, at times, by actual bronchitis. Clinically, the frequency with which respiratory infection follows upon exposure to cold and wet and the increased incidence of pneumonia during the winter months, among outdoor workers, and in regions where there is a wide daily variation of temperature and humidity, are suggestive facts. But it is probable that the direct influence of cold has been overestimated, and its relation to subsequent respiratory inflammation may be more casual than causal. That it is not always a vital factor is evidenced by the rarity of respiratory disease among the members of Arctic exploratory expeditions and among those who live in cold, sparsely inhabited regions.

It may well be true that many of the cases of pneumonia that occur after chilling are dependent upon autogenous infection with pneumococci harbored in the mouth, in contrast to the more general mode of infection with the more virulent strains acquired by contact with pneumonic patients or with carriers.

CLIMATE AND SEASON.—The incidence of pneumonia shows a marked seasonal variation. It is greatest in the winter and early spring; less than twenty per cent. of the cases develop in the summer, and an equal proportion in the autumn. The most important climatic conditions are abrupt changes in temperature and humidity, but the exact influence exercised by cold and moisture is poorly understood. The greater incidence of the disease in winter and in cold climates is undoubtedly influenced by the indoor life with resultant increase in the opportunity for contact infection and, perhaps, to the increased consumption of alcoholic drinks.

ALTITUDE.—The older view that altitude influences the morbidity and mortality rate of lobar pneumonia has been disproved by the statistics of the United States Army. It is said that cardiac complications are more frequent among those who live at high altitudes and intestinal complications more usual among those who live near sea level.

Sex.—Lobar pneumonia under ordinary conditions of life is more than twice as common in men as in women. That this difference of incidence is due to environmental conditions and to different degrees of exposure rather than to any especial susceptibility of the one or resistance of the other seems clear, for the higher incidence in the male is less evident in childhood and is not noted in institutions where the two sexes live under like conditions.

Age.—Pneumonia occurs at all ages but is most common between the ages of twelve and thirty-five years. Instances of congenital pneumonia are recorded. The mortality is greatest at the extremes of life.

Race.—The morbidity and mortality are higher in the negro than in the white race, but it is not established whether this difference is due to a distinct racial character, to the lack of an inherited or acquired immunity to infection, or to the poor hygienic conditions in which the negro lives. That the lack of an inherited immunity or the absence of immunity acquired by frequent minimum infections may be a vital factor is evidenced by the incidence of pneumonia among recently imported workers at the Panama Canal Zone, in the mines of the Rand, Africa, and by the decimation caused by the infection of Esquimaux and Lapps who migrate to temperate zones.[1]

Occupation.—In cities, the incidence is greater among those who labor out of doors than among indoor workers. This difference cannot be explained on the basis of exposure alone, however, for it is not observed in rural communities. It may be dependent in part at least upon the class of workers in the contrasted occupations and on the poorer hygienic living conditions, with overcrowding and filth in the homes of the former group. The mortality is higher among indoor workers. Further, the susceptibility of newly inducted troops as compared with seasoned soldiers may be due as much to the overcrowding in the barracks or tents as to the unaccustomed exposure.

Toxic Agents.—Lobar pneumonia has been known to develop following the inhalation of various irritating vapors, gases and the aspiration of different fluids. The action of these various substances may be in part mechanical, opening the way for infection. It would be interesting to study this group with reference to the incidence of pneumonia due to Type IV pneumococcus, for it is not improbable that the disease that results is dependent upon autogenous infection with the type organism already present in the buccal secretion. Again it may be true that only those individuals who are carriers of the more usually pathogenic types develop the disease.

The rôle of dust as an infecting agent has been demonstrated by Stillman,[2] who isolated virulent pneumococci from the dust of the environs of patients ill with pneumonia.

Overexertion and worry are predisposing factors only when so prolonged or marked as to cause general reduction of bodily nutrition.

TRAUMA.—True lobar pneumonia following trauma is exceedingly rare. It is most apt to follow crushing injuries of the chest wall or a direct blow with or without penetration of the thorax. The symptoms usually develop within a few days of the injury and the sputum is often more hemorrhagic than is the rule in the cases arising in the usual way.

PREGNANCY.—The relative infrequency of lobar pneumonia during pregnancy may be due to the limited exposure of pregnant women to infection, to the relatively low incidence in women, or to a form of resistance the nature of which is not understood.

PREVIOUS ATTACK.—One attack of pneumonia creates a predisposition to subsequent infection, a fact well shown by Norris's statistics, according to which a history of previous pneumonia was obtained in 13.6 per cent. of the cases analyzed. Several attacks are by no means uncommon, and as many as 28 are said to have occurred in one individual.

ALCOHOLISM.—It is questionable if alcoholism is an important predisposing factor, except when it is excessive. The increased incidence of pneumonia among alcoholics is probably due more to exposure, general habits of life, etc., than to any direct influence of the alcohol itself.

ASSOCIATION WITH OTHER DISEASES.—*Typhoid fever* and lobar pneumonia rarely coexist. The term typhoid-pneumonia should be restricted to designate pneumonia due to the *Bacillus typhosus* and not applied to pulmonary consolidation of different causation.

Influenza is frequently complicated by the development of pneumonia and the mortality is enhanced greatly thereby. The consolidation is usually lobular, often pseudolobar, occasionally true lobar in type. These pneumonias may be due to the streptococcus, the pneumococcus (most often Type IV) or to the influenza bacillus.

Pulmonary tuberculosis, according to Flick's statistics,[3] is preceded by an attack of lobar pneumonia in nearly one-fifth of the cases studied. In the writer's opinion, such an association is far less common, for careful analysis of the history will often disclose the fact that the acute initial symptoms were not due to a pneumococcus infection but to a subacute, tuberculous lesion clinically indistinguishable at the time from lobar pneumonia. Apical pneumonia and cases of delayed resolution may be confused with tuberculosis. Pneumococcus pneumonia is an uncommon complication of phthisis, and though it may not influence the course of many cases, it often leads to a recrudescence of a quiescent lesion and, perhaps, to the development of disseminated tuberculosis.

When lobar pneumonia develops in the course of *diabetes mellitus,* it has an exceedingly high death rate, and in these cases gangrene of the lung is a more frequent complication than it is otherwise.

In other chronic diseases pneumonia is a very usual terminal event, but it is much more frequently of the lobular than the lobar variety. When true lobar pneumonia does occur the onset is insidious, the course atypical and the mortality rate unusually high.

The relation of *focal infections with the pneumococcus* to the development of pneumonia has not been sufficiently studied. That there may be an important etiological relationship is evidenced by the cases of two patients, each with a chronic infection of a paranasal sinus due to Type II pneumococcus—both of whom developed subsequently a lobar pneumonia due to the same type organism.

Exciting Cause: the Organism.—The synonyms for this organism, as designated by various investigators, are: *Micrococcus pasteuri* (Sternberg), *Diplococcus pneumoniæ* (Weichselbaum), Pneumococcus (Fränkel), *Microbe septicemique du salive* (Pasteur), *Micrococcus lanceolatus.*

Weichselbaum[4] pointed out the fact that pulmonary consolidation may be caused by many different organisms, but the overwhelming frequency with which the pneumococcus occurs as the cause of lobar solidification of the lungs has led to the restriction of the term "lobar pneumonia" clinically to describe the disease due to that particular parasite.

This article deals only with pneumonia due to the pneumococcus. A consideration of the diseases due to infection of the lungs with various other microörganisms will be found in other sections.

In 1880, Sternberg isolated an encapsulated diplococcus from his own saliva, with which he produced a fatal sepsis in rabbits. Almost at the same time and independently, Pasteur made a similar discovery in the saliva of a child with rabies. Neither recognized the pathogenic properties of the organism at that time and it is to Eberth,[5] but more especially to Fränkel,[6] that the credit is due for indicating the relationship of pneumococcus to pneumonia.

Fränkel demonstrated its frequent occurrence in lobar pneumonia, described its pathogenic and biological characteristics and gave it the name by which it is most generally known. His findings were confirmed and elaborated by Weichselbaum, who identified the pneumococcus in the blood and the tissues of a large series of cases of pneumonia.

1. MORPHOLOGY.—The pneumococcus is typically a diplococcus; the individual members of each pair of cocci are lancet shaped with flat surfaces opposed, but marked variations of size and shape are often noted, so that oval and bacillary forms may be seen in the same or in different cultures. In young actively growing cultures in fluid media chain formation may occur, but it is rarely seen when the growth is more sluggish and on solid media. In old cultures involution forms may scarcely be recognizable as the pneumococcus and even the characteristic staining reactions may be lost.

The organism is encapsulated, non-motile and does not form spores. The capsule is most readily demonstrated in freshly isolated strains or when the young growth on suitable enriched media is examined. It appears as a halo about the cocci, and is pale or stained, depending upon the method of demonstration utilized. The capsule is most voluminous in the Type III *Pneumococcus mucosus,* and is well developed in recently isolated virulent strains of Type I and Type II, whereas in Type IV, though sometimes well formed, it may be scanty or absent. The function of the capsule is not definitely understood, though it is thought to be protective and may be an index of virulence.

The pneumococcus stains readily with the ordinary aniline dyes and is not decolorized by Gram's method (it is Gram-positive).

2. Cultural Characteristics.—The organism can be grown on ordinary culture media but is very sensitive to variations in reaction and composition. Optimum conditions for luxuriant development are found when the media are prepared directly with infusion of beef, when sterilization is accomplished by the Arnold method, and when the reaction is neutral or from 0.3 to 0.5 acid to phenolphthalein. The optimum temperature for incubation is 37° C. (98.6° F.), but growth will take place at a temperature as low as 25° C. (77° F.) and as high as 41° C. (105.8° F.) Its thermal death point is 52° C. (125.6° F.) for ten minutes. It is a facultative anaërobe and is not sensitive to changes of oxygen tension On media prepared with beef extract, the growth is scanty and poor, but on meat infusion agar enriched with blood the colonies are round, moist, discrete, translucent with well-defined edges. The center of the colony is darker than the granular periphery and the growth is surrounded by a zone of greenish discoloration.

The growth in broth is diffuse, leading to uniform turbidity of the medium; but after twenty-four hours, as autolysis of the cocci occurs, the clouding clears. No pellicle forms, but there is flocculent sedimentation.

Gelatin is not a suitable medium for cultivation of the organism, but when pneumococcus is grown upon it, no liquefaction occurs.

In milk and in inulin-serum water the pneumococcus forms acid, with consequent coagulation of the medium. Fermentation of inulin is a characteristic property of pneumococcus utilized in the identification of the organism. Inasmuch, however, as some strains do not ferment inulin, and others ferment it only at times, the test is only of confirmatory value and negative results are of little worth.

On media enriched with simple carbohydrates, the initial growth of pneumococcus is increased, but due to acid formation resulting from fermentation of the sugars, growth is inhibited early. The addition of calcium carbonate to such media will prolong the period of growth.

3. Differential Cultural Reactions.—The pneumococcus is often difficult to differentiate from some strains of streptococcus and to distinguish them certain cultural tests are especially helpful.

Colonies of pneumococcus on blood agar are surrounded by a green zone of methemoglobin.

Pneumococcus generally leads to fermentation of inulin, whereas streptococcus does not. Pneumococcus rarely causes precipitation in serum glucose agar (0.5 per cent. glucose and ascitic fluid with a specific gravity of 1.015 or more), whereas streptococcus regularly does. The pneumococcus undergoes solution in bile due to the presence of cholic acid (Neufeld), whereas the streptococcus is not dissolved. This bile solubility test is recognized as a valuable differentiating character of the pneumococcus. The test may be carried out with whole bile or with a 10 per cent. solution of sodium taurocholate or sodium glycocholate in 0.85 per cent. salt solution. One-fifth to one-tenth volume of bile will cause solution of an actively growing broth culture of pneumococcus. The presence of serum inhibits the reaction, and avirulent strains are less constantly dissolved than are virulent ones.

The *Pneumococcus mucosus* forms a more abundant, confluent, heaped-up sticky growth on the surface of solid media that characteristically "strings out" when a needle is raised from its surface. It is distinguished from *Streptococcus mucosus* by its solubility in bile, its power to ferment inulin, the greenish discoloration of blood media caused by it, and its virulence for mice.

In brief, certain characteristics of the pneumococcus serve to differentiate it from allied organisms, especially the streptococcus. Finally, the specific reactions of various strains of pneumococci with their homologous immune sera definitely establish their identity.

4. Viability.—The life of pneumococcus on artificial media is relatively short, and unless frequent transfers are made or special methods are employed the organism rapidly dies. Kept in the ice chest, cultures in blood broth may remain viable for several weeks and if the spleens of infected mice are dried *in vacuo* and kept in the dark, the organism may be recovered by animal inoculation after a period of months.[7] Even on suitable media the pneumococcus sometimes fails to grow, but this is unusual if infected blood is added. Recent transfers to meat infusion broth grow poorly, but with frequent transplanting the organism grows more readily. Chesney has shown that transfers made during the period of maximum growth multiply readily and without the period of lag characteristic of older cultures.

5. Virulence.—The virulence of the pneumococcus varies greatly. It is increased by passage through susceptible animals and attenuated by prolonged artificial cultivation. Recently isolated strains are usually very virulent for susceptible animals but virulence is a relative term and varies for different hosts, so that an estimate of the infectivity of the organism for one animal is not necessarily a measure of its invasiveness for another. It is only generally true that a given strain of pneumococci virulent for man will be virulent for mice, and *vice versa.*

To what extent the increased or decreased incidence of pneumonia is dependent upon variations in the virulence of the pneumococcus has been the subject of much discussion. The fact that the invasive power of the organism may be enhanced by passage through animals and lessened by prolonged artificial cultivation offers some support for this idea. But virulence is *not* absolute; it is relative to and dependent upon the resisting power of the host which may vary as widely as the invasive ability of the organism. Outbreaks of pneumonia are surely determined as much by variations in the susceptibility of the invaded as by the virulence of the invader—a fact admirably illustrated by the case of healthy carriers who may harbor pathogenic types of the pneumococcus without developing pneumonia.

6. Toxin Formation.—It has not been shown that the pneumococcus forms a true soluble toxin and the manifestations of pneumococcus infection are variously attributed to the action of liberated endotoxins, to intoxication with poisonous split products resulting from the disintegration of bacterial protein, and to the products set free by the metabolic activities of the organism itself. Autolysates of the cocci are hemo-

lytic and toxic, and though both of these properties are lessened by the action of immune serum, neutralization is not complete nor is it absolutely specific. Both the lytic and the anaphylotoxic action vary with the virulence of the organism and both are thermolabile, removed by filtration through a Berkefeld filter and by tryptic digestion. According to Dochez and Avery, the hemotoxin exists preformed in the bacterial cell as a hemolytic endotoxin.

Recently these observers have confirmed and extended the observation of Kraus[8] on the formation by the pneumococcus of a soluble substance in culture media. This specific precipitable substance found in the cell-free fluid of young cultures is demonstrable not only *in vitro,* but is present also in the blood and urine of infected animals and of patients with pneumonia. It is thermostabile and is not destroyed by precipitation with alcohol, ether or acetone, or by digestion with trypsin.[9] The demonstration of this substance in the blood and urine of infected individuals is of real diagnostic and prognostic value, and when it is excreted in large amounts is a sign of unfavorable import. To what extent this precipitable substance may be responsible for the intoxication present in infections with pneumococcus is not established.

7. BIOLOGICAL CLASSIFICATION.—Neufeld and his co-workers first clearly indicated that groups of pneumococci could be differentiated from one another by their immunologic reactions, and Dochez, Cole and his associates at the Hospital of The Rockefeller Institute established the differentiation of the species into four definite types. Lister has further refined the classification.

The classification is made on immunological and cultural tests and on morphological characters. Pneumococci isolated from numerous cases of pneumonia were studied; animals were immunized to each of many strains; and the immunity reactions of all were tested against each serum thus obtained. Agglutination, precipitation and protection experiments clearly established the existence of at least four groups of organisms arbitrarily designated Types I, II, III and IV. Individual members of Types I and II show no distinctive morphological or cultural properties, but each possesses immunologic characters common to other members of the homologous group and different from those of other groups. Many atypical strains of Type II have been studied but the significance of this finding is not established. Type III is the *Pneumococcus mucosus* and it is distinguished from the other types by morphologic and cultural differences as well as by immunologic reactions. All members of this type provoke a common immunity response.

Type IV consists of heterogeneous strains that are not interrelated, and only small groups of this type have common immunologic properties.

Types I, II, and III include about 80 per cent. of all strains responsible for infection in man. Type IV includes about 20 per cent. of the strains isolated from lobar pneumonia and is the variety generally found in the buccal secretions of normal individuals.

PNEUMOCOCCUS *Type*	INCIDENCE *Per cent.*
I	33.3
II	29.3
II Atypical	4.2
III	13.0
IV	20.3

From this table of Avery, Chickering, Cole and Dochez,[10] it is seen that Types I and II are the usual cause of infection, and are responsible for over 60 per cent. of the cases of lobar pneumonia studied. Type III is an infrequent cause of infection, and Type IV is the etiological agent in about 20 per cent. of the cases, the incidence of disease due to it varying in different places.

Immunization of horses with strains of Type I or II results in the development of a serum of reasonably high titer. Such sera are efficacious against members of the homologous group, but are without protective value against individuals of the other type. Immunization with Type III has not yielded satisfactory protective serum, and though comparatively potent sera can be developed by inoculations of members of Type IV, such sera protect only against the organism used to produce them and lack the power to prevent the progress of infection due to other members of the same type.

The identification of the particular type of pneumococcus responsible for infection in large numbers of cases has led to a revision of our ideas of the epidemiology of lobar pneumonia and it furnishes a better basis for prognosis and for specific therapy in individual cases.

8. ISOLATION OF PNEUMOCOCCUS AND DETERMINATION OF TYPE.—*A. From Sputum.*—(i) Stained Smear Preparations.—Direct spreads of sputum are stained by Gram's method and with a capsule stain. The pneumococcus is readily recognized by its morphology and Type III may be identified by its very abundant capsule.

(ii) Mouse Inoculation.—The sputum is carefully washed in several changes of sterile salt solution to free it of contaminating organisms and a small bit is then emulsified with sterile broth or salt solution. With aseptic precautions, 1.0 c.c. of this emulsion is inoculated into the peritoneal cavity of a white mouse and as soon as the mouse appears ill, a drop of peritoneal exudate is removed by aspiration; and if smear preparations show very numerous pneumococci the animal is killed and the determination of type is made. If the organisms are few the animal is allowed to live and later test aspirations are made, or the animal is allowed to die. At autopsy the peritoneal cavity is opened with sterile precautions and both cultures and films made from the exudate to prove the pneumococcus is present in pure culture.

The organism should be identified also by cultural tests. The peritoneal exudate from the mouse is washed out with sterile salt solution and the washings are centrifuged at low speed to remove the fibrin and cells. The supernatant bacterial suspension is transferred to another tube and centrifuged at high speed until the pneumococci are sedimented. The fluid is then decanted and the bacterial sediment is taken up in sufficient salt solution to make a suspension of about the opacity of an 18-hour broth culture of the organism. Fractions of this suspension are used for macroscopic agglutination tests, being mixed with dilutions of immune serum in equal quantities. The concentration of serum required will vary with the titer of the serum employed, but it is necessary that the dilution be found which causes agglutination of the homologous type and does not cause cross-agglutination of the other types before a given serum can be utilized in carrying out the test.

The agglutination test is not satisfactory when other organisms are present in large numbers; and when this is the case the precipitin method, as described by Blake, should be utilized.

The peritoneal exudate prepared according to the above technic is immediately centrifuged at high speed until the supernatant fluid is water-clear. The clear fluid is mixed in quantities of 0.5 c.c. with equal quantities of antipneumococcus serum and a specific precipitation promptly occurs in the tube containing the homologous immune serum. This test is consistently positive with Types I, II and III, and negative with Type IV. To identify the atypical strains of Type II it is necessary to use two dilutions of serum in the test. The typical Type II causes precipitation in both diluted and undiluted serum, whereas variants in this type precipitate only the undiluted serum. The precipitin test is not interfered with by the presence of other organisms.

B. From Blood Culture.—Cultures of the blood are made as described, and the organism identified as the pneumococcus. Ten c.c. of the infected blood broth are centrifuged at low speed to remove blood-cells and the supernatant fluid transferred to another tube. This is centrifuged at high speed and the sedimented bacteria are resuspended in sterile salt solution. The type of pneumococcus is then determined by macroscopic agglutination tests.

C. From Spinal Fluid, Empyema and Lung Puncture.—The type of pneumococcus obtained from these sources is determined according to the foregoing methods.

Lung puncture is a procedure to which recourse need rarely be had, but when it is carried out cultures should be made directly in bouillon.

D. Determination of Types of Pneumococcus by Means of Specific Precipitin Reaction in the Urine.—Reference has already been made to the fact that a certain percentage of patients with lobar pneumonia excrete in the urine at some stage of their disease a soluble precipitable substance of pneumococcus origin. This substance gives a specific precipitin reaction with antipneumococcic serum corresponding in type to the organism causing the infection. The test for it does not supplant the usual bacteriological methods, but is useful in that in some cases an immediate diagnosis of type can be made from a study of the urine.

The urine, concentrated or as passed, is centrifuged and when water-clear is mixed in amounts of 0.5 c.c. each with equal quantities of antipneumococcic serum of the various types. A precipitate is formed immediately or after incubation for one hour at 37° C. (98.6° F.). The reaction may be slight or marked. Long incubation should be avoided, as bacterial growth may obscure the result.

9. CARRIERS.—Ever since the observations of Pasteur and of Sternberg, it has been known that the pneumococcus is present in the mouths of many healthy people, but it is only of recent date that the importance of this fact has been appreciated in studying the epidemiology of pneumonia. It is now generally conceded that the types of pneumococcus ordinarily harbored in the buccal secretions of the healthy are the more or less saprophytic Type IV, the infrequent Type III, and atypical Type II, relatively uncommon causes of lobar pneumonia; and that in the healthy the more pathogenic types are not usually found. But often in those convalescent or recently recovered from the disease, in those intimately exposed to patients with pneumonia, and very rarely in a healthy individual who has not been in contact with the disease, the more parasitic Type I and Type II are present. These individuals —and of them more particularly the convalescent and those intimately exposed to the disease—are real carriers, and it is probable that through their agency the disease is often spread.

10. EPIDEMIOLOGY.—Epidemics of pneumonia are not uncommon and the statistics collected by Wells admirably indicate the special peculiarities of many of those that have occurred. The reported outbreaks were noted most commonly in the winter and spring, and were rarely extensive, except in barracks, prisons and hospitals.

The epidemiological studies of Stillman indicate that the disease is spread directly through contact of the healthy with patients ill with pneumonia, with carriers healthy and convalescent, and through infected dust; and they emphasize the need of isolation to prevent the dissemination of the disease.

11. PNEUMOCOCCUS IN APPARENTLY HEALTHY INDIVIDUALS.—Extensive observations have shown that the pneumococcus occurs in the buccal secretions of the healthy in from 15 to 85 per cent. of all cases examined. Longcope and Fox showed a low incidence for November, an exceedingly great increase in December and January, and a slow return to a low incidence in March and April.

The frequency with which pneumococcus occurs in the saliva is independent of the place of residence and the kind of occupation but, according to Buerger, the organism is found more often in males than in females.

Dochez and Avery [11] showed that a large percentage of individuals in intimate contact with active cases of lobar pneumonia, due to infection with Types I and II pneumococci, harbor in their buccal secretions organisms of the type responsible for the disease. They likewise demonstrated the infrequent occurrence of these highly parasitic types in any except those exposed to infection or convalescent from pneumonia.

Stillman,[12] in elaborate epidemiological studies based on these findings, studied the saliva of 942 healthy individuals, some in contact with lobar pneumonia. From the saliva of 450 (or 47 per cent.), one or more types of pneumococci were isolated; and from 492 individuals no pneumococci could be recovered at the time of the examination. The appended table summarizes the frequency of occurrence of the various types:

PNEUMOCOCCUS	INCIDENCE	INCIDENCE
Type	*No.*	*Per cent.*
I	34	7.0
II	22	4.5
IIa	1	0.2
IIb	26	5.3
IIx	47	9.7
III	85	17.5
IV	271	55.8
Pneumococcus present....	450	
" absent	492	
	942	

In view of these studies it is clear that Types IV, III, IIb and IIx must be regarded as normal inhabitants of the healthy mouth, and that Types I and II rarely occur in the saliva, except of those convalescent from infection or of those exposed to the disease, lobar pneumonia. The latter fact is borne out by the demonstration of these types in only 0.8 per cent. of the healthy as compared with an incidence of 11.0 per cent. in the mouths of the convalescent or exposed.

These data indicate the epidemiological importance of contact as a means of disseminating the disease and show that it may be spread by associating with patients, convalescents, healthy carriers or through the agency of infected dust.

If autogenous infection with one of the types normally present in the mouth occurs it is due to altered resistance of the host as often perhaps as to enhanced virulence of the micrococcus or to a combination of these two factors.

12. Pneumococcus Outside the Body.—The pneumococcus is a very delicate organism and soon dies outside of the body. Even in cultures it succumbs rapidly unless conditions are optimum. It is readily killed by exposure to sunlight, by treatment with ordinary disinfectants and by heat. In sputum it is fairly resistant.[13] In moist sputum at room temperature and in the dark the organism has an average viability of about fourteen days; in strong light of less than five days. At 0° C. it may live 35 days, but when moist it is killed by exposure to 52° C. (125.6° F.) for ten minutes.

In powdered sputum the pneumococcus dies in from one to four hours, depending upon the exposure to light. In dried sputum in the dark it survives on an average for 35 days; in diffuse light 30 days; but in direct sunlight less than four hours.

According to Stillman, the pneumococcus was demonstrable in the dust of patients' quarters in over 53 per cent. of the cases studied, and in every case the same type was present in the dust as was responsible for the illness. Growth developed in cultures of dust as long as 16 days after the patient was removed from the source where it was obtained, but generally the dust became free of pneumococci sooner than did the saliva of individuals exposed to the disease.

13. Pathogenesis.—The why of infection with and the wherefore of resistance of particular individuals to the pneumococcus are still moot. The usual mode of infection, the route by which the micrococcus reaches the lungs and the reason for the predominantly pulmonary localization of the reaction to invasion are questions still awaiting final decision, and it is probably true that the answers to them differ in individual cases.

The aspiration or inhalation theory is the one generally held and there is much evidence to support it. The frequency with which a respiratory infection antedates the onset of pneumonia, the epidemiological studies of Stillman, the insufflation experiments of Lamar and Meltzer,[14] the instances of so-called anesthesia or aspiration pneumonia, all point to the occurrence of aërogenous transmission. But whether the inhaled pneumococci are drawn directly into the bronchi and, held there by inflammatory obstruction, directly lead to a reaction in the neighboring lung tissue, is to be determined. Granted a primarily aërogenous route of infection, it may still be that aspiration of the organism is followed by a more circuitous transportation of the pneumococcus and that the cocci are taken up by the blood or lymph capillaries of the upper respiratory tract and reach the lung by a hematogenous or a lymphogenous route.

This idea predicates a bacteriemia (not a sepsis) as an antecedent of pulmonary consolidation, and there is evidence that in some cases such a condition occurs. Certainly it is suggested by the finding that positive blood cultures are often obtained when the blood is examined early in the disease, by the sudden onset with chill, by the appearance of constitutional symptoms before the signs of pulmonary disease develop, by the disproportion in some cases between the symptoms and the extent of pulmonary consolidation of the lung, and by analogy with the newer ideas of other diseases, such as epidemic cerebrospinal meningitis.

Further, the occasional occurrence of a primary pneumococcal meningitis or peritonitis shows that the organism may localize elsewhere than in the lung. If this idea is accepted there remains to be explained the predilection of the pneumococcus for the lung—perhaps the result of a definite tissue affinity, perhaps dependent on a preëxisting tissue sensitization, or to some unknown cause.

14. Immunity.—An epidemic and endemic disease, self-limited and usually terminating abruptly, pneumonia apparently offers problems in immunity that should be readily solved, but study has shown the case to be otherwise.

The relative resistance of man to infection with the pneumococcus, as evidenced by the infrequency of a sepsis without metastatic localization, has been attributed by some (Dold) to opsonins and bactericidal substances occasionally present in the serum of normal individuals. But this thesis is negatived by the absence of increased protection in those recovered from pneumonia, in the serum of whom these bodies are more constantly and more abundantly present.

The immunity that develops in favorable cases of the disease is better understood, and study of the phenomena associated with crisis has cast light upon the whole subject of immunity to pneumococcus. It is known that crisis is not due to anatomic changes in the lung or to a sudden loss of virulence of the pneumococcus (Rosenow); that the percentage of positive blood cultures and the intensity of the blood invasion, if present, decrease as crisis or lysis is approached; and that the number of viable organisms that can be isolated from material obtained by puncture of the lung diminishes perhaps even to zero during or after crisis.

The literature abounds with contradictory explanations of the changes responsible for the production of these changes and for the protection produced experimentally in animals.[15-21] According to Clough,[22] the only antibodies that appear in significant quantities are substances that promote phagocytosis. He has shown that serum obtained after crisis causes active phagocytosis of the homologous virulent strain and that with the increased phagocytic power of the serum there is a parallel increase in its power to protect mice against infection with the homologous type.

Inasmuch as the phagocytic activity of such serum parallels its protective power for mice in time of appearance, incidence and in strict specificity, it would seem that the protective power depends upon and is due to its power of producing phagocytosis. To quote Clough:[22]

"The fact that such definite phagocytic activity can be shown to develop at the crisis (or lysis) in at least a considerable proportion of cases and that this activity is directed against and largely limited to the one virulent strain infecting the patient makes it seem probable that this factor plays an important part in bringing about recovery in man.

"The active substances in the serum are bacteriotropins in the sense of Neufeld, since they resist heating at 56° C. (132.8° F.) and persist in the serum *in vitro,* at least for a considerable period."

A state of hypersensitiveness to the protein of pneumococcus has been demonstrated in some cases of pneumonia but its development is inconstant. It does seem, however, that an allergic state may be responsible for many of the manifestations of the disease. The predominantly exudative character of the local reaction, its intra-alveolar, noninterstitial localization and the abrupt onset all resemble the type of response caused by experimental infection in sensitized animals.

Finally, although bacteriotropins, agglutinins, lysins, opsonins and other antibodies may each in varying degree contribute to the immunity against the pneumococcus, it seems not unlikely that the rôle of each may prove relatively unimportant and that some new type of reaction on the part of the host may be found more directly responsible.

SYMPTOMATOLOGY

General Course of a Typical Case.—The disease usually sets in abruptly, generally with a rigor. This is of variable duration, occasionally lasting an hour or more. During it there is apprehension, the teeth chatter, there is generalized shivering, the patient complains of feeling cold and is so ill he takes to bed. The chill gradually subsides and in place of a feeling of cold a sensation of unbearable heat comes on. The skin and mucous membranes, pale during the rigor, become flushed and red, a throbbing headache often develops, and either torpor or delirium may appear. There is anorexia and oftentimes vomiting. The temperature is elevated and may rise to 104° or 105° F. (40° or 40.6° C.).

Usually at onset or after the rigor there is intense thoracic pain increased by respiratory effort—deep breathing, laughing, coughing, yawning or sneezing—so severe as to cause cessation of all voluntary activities. The respirations are rapid, superficial, often slightly irregular, labored, and interrupted by a dry, hacking cough.

The patient is manifestly ill and the history, with the finding of dyspnea, flushed skin and often cyanosis, bright, glistening eyes, rapid, shallow respiration, expiratory grunt, dilatation of the nostrils with each breath, accelerated pulse, fever, the complaint of thoracic pain and the hacking cough, arouse the definite suspicion of a developing pneumonia. Examination of the lungs, however, may discover only limited expansion of one side of the chest, suppressed breath sounds or a pleural friction rub.

After 24 to 72 hours the thoracic pain diminishes in intensity, the cough becomes productive, leading to the expulsion of characteristic sputum, herpes appears on the lips or other parts of the face, the fever continues at the same or at a higher level, the tachycardia is unchanged and a tympanitic note is elicited over an area of the chest where, too, there may be suppression of breath sounds, crepitation or tubular breathing.

In mild cases these symptoms persist for several days. By the sixth or eighth day they may become more marked, the pulse more rapid and weaker, the cyanosis more pronounced, while outspoken signs of consolidation of the lung that have developed may spread or resolution may begin.

At a varying period after onset, the crisis may occur. The temperature suddenly falls, reaching normal in 10 to 24 hours, beads of perspiration appear on the face, and soon the entire body is bathed in a copious sweat. Respiration becomes easier, slower, less labored, the color improves and the disagreeable symptoms associated with fever disappear. The sensorium clears and the patient passes from a state of extreme illness and discomfort to one of comparative well-being.

In more severe cases crisis fails to develop, dyspnea and cyanosis increase, the temperature continues high or, though it fall even to normal, the condition of the patient does not improve. The pulse becomes more rapid and weaker, restlessness and anxiety develop and collapse follows.

In other instances crisis is delayed or never occurs, and a case with mild symptoms may suddenly develop very grave and untoward manifestations.

Clinical History.—INCUBATION PERIOD.—The period of incubation is not definitely established. It is probably short and is variously estimated at from one to eight days. Of especial value in the determination of the time for incubation are the cases in which pneumonia follows trauma. In observed instances, the time between the injury and the chill of onset has varied from a few hours to one or two days.

PRODROMAL SYMPTOMS.—Prodromal symptoms are generally lacking, though not infrequently a history is obtained of antecedent thoracic pain, anorexia, headache, lassitude, an acute bronchitis, vomiting, tonsillitis, joint and muscle pains, epistaxis, abdominal pain, etc.—none of which is characteristic. The most common prodrome is a mild acute respiratory infection. The frequency with which such a history is obtained will depend in large measure upon the care with which the investigation is made.

ONSET.—The onset with chill is by far the most frequent. According to Norris,[23] of 9,851 cases, 58.18 per cent. had a rigor; of 2,334 cases, 30.12 per cent. had chilliness; of 217 cases, 12.44 per cent. had repeated rigors. Jurgensen states that 60 per cent. of all cases have either a chill or chilly sensations at the onset.

The presence or absence of this symptom depends upon the individual attacked. It is uncommon in children, in whom a convulsion is of more frequent occurrence; and in the aged, asthenic or alcoholic, it is often lacking. In the latter the onset is gradual in about half of the cases.

The rigor of onset may last as long as nine hours (Nothnagel) and it may be repeated.

SYMPTOMS DURING PROGRESS OF DISEASE.—(*a*) *Fever.*—During or just after the initial chill the temperature rises abruptly and reaches its summit on the first or second day. In cases that have no chill at onset the temperature may rise rapidly, but occasionally the ascent is slower and may continue 3 or 4 days before attaining a maximum.

As a rule, the fever remains at a fairly constant level from onset to crisis with small remissions of 0.5°-1° F. (0.3°-0.5° C.) in the twenty-four hours. The average maximum is 103° F. (39.4° C.), though in many cases a higher level is maintained and a temperature of 105° or 106° F. (40.5° or 41.1° C.) is not uncommon.

Instead of a continued or subcontinued elevation of temperature, the fever may be outspokenly remittent, with a daily range of 1.5°-3° F. (0.8°-1.6° C.). Less often an intermittent fever with oscillations of 4 or more degrees above and below the base line is seen.

A relapsing type of fever has been described (Wunderlich). It was formerly seen in patients treated by repeated liberal venesections.

Abrupt exacerbations of fever sometimes occur, accompanying the spread of the inflammatory process to portions of lung hitherto uninvolved, and similar rises, apparently independent of any extension of the disease, occur.

A sudden fall of temperature with collapse may occur at any stage of the infection and is to be differentiated from a pseudo-crisis by the associated physical signs (poor quality of the pulse, appearance of the patient, etc.).

Pseudo-crisis is a term used to describe a marked abrupt lowering of the temperature occurring, as a rule, one to three days before the true crisis, and accompanied by an improvement in the general condition of the patient. It is distinguished from a *real crisis* by less marked slowing of the pulse rate, and by a subsequent rise of temperature within 24 to 48 hours. Pseudo-crisis occurs in about 10 per cent. of all cases of pneumonia.

Defervescence in typical uncomplicated cases is by crisis. The fall of temperature comes on abruptly from a maintained high level or from some point in a scale of gradual descent and reaches normal within 24 hours. Occasionally the crisis is preceded by a slight or a marked exacerbation of fever. If the fall to normal requires more than 24 hours it is termed a *protracted or delayed crisis;* if more than two days elapse, termination of fever is said to be by *lysis.* The critical fall in temperature begins most often in the evening or during the night and may be extremely rapid. The writer has seen a fall of 4.5° F. (2.5° C.) in six hours.

The day of disease on which *crisis* occurs varies greatly. Traube's dictum that it occurs only on the odd days—third, fifth, seventh, ninth, eleventh—has long been discredited, and collaborated statistics show a nearly equal incidence on the odd and even days. Crisis, as early as the beginning of the second day and as late as the sixteenth, has been observed by the writer. It has been known to occur later than the twentieth day (Norris), but most commonly it occurs between the fifth and the thirteenth.

After crisis, a subnormal temperature may persist for several days, but hypothermia is much less common than in convalescence from typhoid fever. Marked postcritical elevations of temperature, except in association with a complication, are rare; but it is the rule for days or weeks after crisis has taken place to have an elevation to 99° or 99.5° F. sometime in the twenty-four hours. These slight elevations are perhaps associated with absorption from the resolving exudate in the lung.

When defervescence has not been established by the 14th day it is apt to take place by lysis. Lysis occurs in about 20 per cent. of all cases, and is especially common in the aged and in secondary pneumonias.

Unusual grades of hyperpyrexia (107°-109° F.) (41.6°-42.8° C.) have been recorded in association with marked nervous symptoms and just before or even after death. Parkinson[24] reported a case of pneumonia without nervous symptoms in which a temperature of 110° F. (43.3° C.) was recorded on the 5th day of the disease and an elevation of 105° (40.5° C.) for four days, after which crisis occurred.

(*b*) *Thoracic Pain.*—Thoracic pain is the most constant local symptom of pneumonia occurring in about 90 per cent. of all cases (Grisolle).

It is frequently the initial symptom, antedating the chill of onset by several hours; it often begins during the rigor or it may rarely develop in the course of the first days of the attack. It is most intense during the early hours and usually disappears within the first several days. The very prompt subsidence of the pain is occasionally an unfavorable sign, indicating the development of a pleural exudate.

The pain is a typical "stitch in the side" associated with inflammation of the pleura. It is variously denoted as intense, sharp, stabbing or lancinating, and is so agonizing that the patient voluntarily shortens the depth of inspiration. The severity of it is not an index of the gravity of the disease, though oftentimes it is of maximum grade in the severer cases.

The pain is rarely diffuse but is localized in a portion of one side. It occurs most commonly in the lower axillary or in the mamillary region, but may appear in any part of the chest or shoulder. There is at times hyperesthesia of the skin over the painful area and circumscribed pressure increases the pain, whereas broadly applied pressure often relieves it. The reason for the apparently paradoxical influence of pressure is probably the fact that the wider application, by limiting expansion, lessens the mobility of the lung.

In children pain is often absent, though at times it may be exquisitely severe. In the aged, the asthenic, the alcoholic and the delirious it is often wanting, and in central and in apical pneumonia it is a very unconstant symptom.

The cause of the pain is probably not pulmonary in origin, as evidenced by its absence in extensive disease of the lungs (neoplasm, deep abscess, etc.), but it is usually ascribed to the inflammation of the pleura associated with the pneumonia.

The pain may be migratory in character; it may be referred to the uninvolved side of the chest, to the shoulder, neck, arm or abdomen.

(*c*) *Abdominal Pain.*—Abdominal pain is not uncommon in pneumonia.[25, 26] The importance of the recognition of it as a symptom of this disease cannot be too strongly emphasized, because of the errors of diagnosis to which ignorance of this fact may lead. The pain may be referred to the upper or lower quadrants of the abdomen and it has unfortunately happened often that the source of it has been misinterpreted. More than a few patients with pneumonia have undergone laparotomy for a suspected appendicitis, cholecystitis, cholelithiasis, peritonitis, etc., when subsequent events have clearly shown the abdominal symptoms were due solely to the intrathoracic disease. The coincident presence of rigidity and even of spasm of the abdominal muscles may make differential diagnosis extremely difficult, but a carefully taken history and the presence of rapid, shallow respiration, cyanosis, herpes labialis, etc., will usually disclose the cause of the symptoms.

Chatard,[27] in his analysis of 658 cases at the Johns Hopkins Hospital, noted the occurrence of abdominal pain in 77 per cent.

The cause of the abdominal pain is generally attributed to the existence of a diaphragmatic pleurisy.

(*d*) *Respiratory Tract.*—*Tachypnea*[28] is practically an invariable accompaniment of lobar pneumonia and whenever—especially during the winter months—it is noted, pulmonary consolidation should be suspected. The respiratory rate is accelerated to rates varying from 20 or 24 to as high as 80 or 90 breaths per minute, and to as high as 200 in infants. The average for adults is between 24 and 40 in an attack of moderate severity, and when a rate of more than 50 to 60 per minute is encountered in an uncomplicated case, it is a cause for apprehension. The respirations are rapid, shallow, the patient grunts with each expiration, speech is difficult, and the alæ nasi actively play.

Accompanying tachypnea there is nearly always *dyspnea* of greater or less severity. When dyspnea is present to a degree out of proportion to the extent of the consolidation it is a sign of grave omen.

Rapid and difficult breathing, when occurring in association with great pain and marked psychomotor agitation, are less significant than when signs of cardiac embarrassment are present.

The tachypnea and dyspnea are due to a combination of factors. Pain causes voluntary and involuntary restriction of respiratory effort, thereby hastening breathing and rendering it difficult. Toxemia, cyanosis and nervous symptoms also play a rôle. The influence of the extent of pulmonary involvement is still moot. Undoubtedly it is of some moment, but the observations of Washburn on experimentally infected mice, the results of postmortem studies in many cases, of intravitam examinations in others, and the disappearance of these symptoms after crisis while the consolidation is still unchanged indicate it is not the determinant of their existence except perhaps in bilateral pneumonia.

Finally, the rôle of acidosis as a cause of the polypnea and dyspnea seems established. Lewis[29] and his co-workers have definitely shown that an acidosis due to non-volatile acids is responsible for these symptoms in the cases without cyanosis and to a lesser degree is causal in those with cyanosis. They showed that in pneumonia and in extrapulmonary pneumococcal lesions the alveolar air has a high oxygen content, a low percentage of carbon dioxid, and an increased hydrogen-ion concentration due to non-volatile acids in the blood. Such acidosis, when of mild grade, persists over the crisis, to vanish hand in hand with the breathlessness as convalescence is established. These observations also indicate that the respiratory symptoms of pneumonia cannot be attributed solely to the extent of lung damage.

Cheyne-Stokes breathing is an untoward symptom that occurs especially in the cases with grave toxemia and cardiac failure.

Cough is generally present from the onset and, when bronchitis precedes the chill, is present before it. At first it is unproductive and occurs in paroxysms but it soon becomes frequent, is accompanied by great pain, and every effort is made to suppress it. Later in the course —and especially after crisis—the paroxysms are more prolonged, easier and more productive.

Frequently recurring paroxysms harass the patient, causing pain, restlessness, anxiety and loss of sleep. The violent muscular efforts lead to muscle soreness, and throw a severe strain on the right heart. When the cough is especially violent it may lead to exhaustion and collapse.

Cough is more frequent in pneumonia of the lower lobes; it is less constant or even lacking in secondary pneumonia and in pneumonia of the aged, the very young, the alcoholic and very delirious patients.

Cough persisting or developing after crisis is sometimes indicative of a developing pleural exudate, especially empyema.

Sputum.—In no other disease, except bronchial asthma, are the gross properties of the sputum and the cycle of changes through which it evolves so characteristic as in lobar pneumonia. Especially when bronchitis precedes the onset of an attack, the sputum is mucoid and abundant for the first four or five days. Then, as the inflammatory process spreads and leads to involvement of the alveoli of the lung, it becomes bloody, due to the presence of red corpuscles. Soon it becomes so characteristic as to be diagnostic. Rusty, homogeneous, transparent and extremely tenacious, it must often be wiped from the lips and clings to the inverted container into which it is expelled. Blood is constantly present, uniformly mixed with the mucoid material, rarely in streaks. Occasionally, the sputum is pure blood. The amount varies considerably but, according to Emerson, 150-300 cubic centimeters is the daily average.

The color is a rusty yellowish-brown, but it may be yellow, green, orange, etc., as the hemoglobin derivatives that give it color undergo oxidation. The fact that the sputum may be green or yellow in any case of pneumonia should limit the use of the term "jaundiced sputum" to the cases in which icterus is manifest.

At the time of crisis the sputum becomes less tenacious, more abundant and mucopurulent in character, and the pigmentation progressively fades until a white mucus is expelled. The quantity raised during the disease is small, indicating, as do metabolic investigations, that most of the exudate is absorbed and not expectorated.

Microscopically, smear preparations show a field in which there are swollen red corpuscles in various stages of preservation, columnar and pavement epithelial cells, polymorphonuclear and mononuclear leukocytes and oil droplets. Pneumococci, both extracellular and intracellular, are numerous, and decrease after crisis. The isolation of pneumococci in pure culture from the washed sputum in a given case is strong evidence that the organism is the causal agent of the disease.

Chemically, there is an increase in protein substances, especially albumin, an increase in the fixed salts, more potassium than sodium compounds and an absence of alkaline phosphates.

Variations in Sputum.—Occasionally the sputum is not rusty but is "bloody" throughout the course. Hemorrhagic sputum is seen when pneumonia complicates or is complicated by chronic passive congestion of the lungs and in traumatic pneumonia. When it is expectorated in an apparently uncomplicated attack the suspicion of a tuberculous origin should be aroused, and pulmonary infarct should be considered.

Only in rare cases of uncomplicated lobar pneumonia is pure blood expectorated in large amounts.

Prune juice sputum, so called because of its color and fluid consistency, is occasionally raised and may indicate the onset of pulmonary edema, a severe type of the disease, the beginning of resolution, or occasionally the development of gangrene of the lung.

The expectoration of *green sputum* may have no especial significance, but it occasionally indicates an incorrect diagnosis, or a developing complication. It occurs in uncomplicated pneumonia, in pneumonia with jaundice, in delayed resolution and in abscess of the lung. In no case in which it is a persistent finding ought careful repeated search for tubercle bacilli be neglected.

A very foul odor to a fluid, *brown sputum,* especially if it contains tissue fragments, may indicate gangrene of the lung.

In *pneumonic sputum* plugs and casts of fibrin are quite frequently found. They vary from small, rolled threads of coagulated fibrin to large, branching forms, and even perfect casts of bronchi may be expelled.

(*e*) *Circulatory System.—Cyanosis.*—Slight cyanosis is an almost constant finding in pneumonia, but intense grades do not occur in over 10 per cent. of collected cases.

When cyanosis occurs early in the course of an attack it is a grave prognostic sign. It is especially marked in secondary pneumonia, in individuals with emphysema or cardiac disease; in the course of complications (dilatation of the right heart, endocarditis, pericarditis, etc.); in the alcoholic and aged; and following the prolonged administration of coal-tar derivatives.

The old view that this sign is due to deficient aëration of the blood, resulting from the diminution of respiratory surface, is no longer tenable, in spite of the often noted parallel between the degree of the cyanosis and the extent of the consolidation, and the observation in two cases of a diminished oxygen content of the blood with an increase of the carbon dioxid. Peabody [30] has shown that in most cases of uncomplicated pneumonia the decrease of respiratory surface is completely compensated and the oxygen content of the blood is within normal limits; that the blood often shows a low content of both oxygen and carbon dioxid; and that in the blood of cases with marked bacteremia and of individuals who did not die with great suddenness there is, in addition, a diminished oxygen-combining capacity of the blood similar to that noted in rabbits infected with the pneumococcus and without pulmonary lesions. By experiments *in vitro* and from studies of the blood of rabbits infected with pneumococci, Butterfield and Peabody demonstrated that these changes result from the conversion of hemoglobin to methemoglobin by the direct action of the pneumococcus, and by analogy it is fair to assume that a similar process in man may account in part for the cyanosis and in some instances may explain a lethal result.

Pulse.—The normal ratio between respiration and pulse is 1.0 : 4.5, but in pneumonia this proportion may be 1 : 3, 1 : 2 or even 1.0 : 1.5.

During the chill the pulse is small, rapid and hard. After the rigor it is usually full and bounding. It remains accelerated during the course of the disease, in cases of moderate severity varying between 105 and 115, but in severe attacks, in children, the aged, and when complications develop it may be much more rapid. In the very young a rate of 200 is not uncommon, but when in an adult a tachycardia of more than 125 is met with it is a grave prognostic sign. Mackenzie states, "I have rarely seen an adult patient with a pulse over 140 recover." The rate alone, however, is not a good index for prognosis unless the other characteristics of the pulse be duly considered. The pulse rate is more rapid in women than in men, in the small than in the large. Increased frequency of the pulse at the onset is not so unfavorable as if it develops in the course of the disease.

During the course of an attack the pulse volume is usually smaller than at onset, depending to some extent upon the lessened filling of the left ventricle; and respiratory arhythmia is fairly frequently encountered. Dicrotism is uncommon. A soft pulse often is indicative of a lesion of the myocardium.

Arhythmia before crisis, no matter how infrequent, is regarded by Mackenzie as a very ominous sign. "In all cases of lobar pneumonia that I have met, when the pulse showed even an occasional irregularity before the crisis was reached, death supervened."

With crisis the rate decreases proportionately with the fall in temperature and not infrequently an actual bradycardia is present during convalescence. When the myocardium has been injured, when complications develop, in the neurotic and in patients with hyperthyroidism tachycardia persists.

Blood-pressure.—The changes of blood-pressure in pneumonia have been much discussed.[31-33] Weigert[34] decided from a review of the literature that no conclusions concerning its variations could be established. At direct variance with this view is that of G. A. Gibson,[35] who formulated what has since been known as Gibson's rule: "A pressure appreciably below the normal in pneumonia is invariably of evil omen and any considerable fall bodes disaster. When the arterial pressure, expressed in millimeters of mercury, does not fall below the pulse rate, expressed in beats per minute, the fact may be taken as of excellent augury, while the converse is equally true."

This dictum met with almost universal acceptance until the observations of Newburgh and Minot[36] appeared, which showed that the assumption that the blood-pressure is abnormally low in fatal cases of pneumonia is incorrect and, further, that the vasomotor reflexes are normal in these cases. From the results of their observations they conclude that prognostic inferences based on the relation of systolic pressure to the curve of the pulse-rate are more often incorrect than correct.

From clinical experience the following statements are warranted. The blood-pressure is frequently lowered during pneumonia, but there are many cases in which, throughout the entire course, a normal pressure is found. The severer cases are more apt to have hypotension than are the mild (Staehelin[37]).

The fall of pressure usually is not marked, though in fatal cases a drop of 70 to 80 mm. of mercury is sometimes seen A decrease of pressure of 10-15 mm. of mercury is without significance, but a gradual progressive fall is evidence of cardiovascular weakness and an indication for treatment. An abrupt fall of pressure greater than 25 mm. of mercury is of grave portent. There is no characteristic alteration of blood-pressure associated with the febrile crisis.

Heart.—To make a satisfactory prognosis and to treat lobar pneumonia efficiently, it is essential that careful and accurate observations of the condition of the heart be made from the outset.

The location of the point of maximum impulse, the determination of the right and left limits of cardiac dullness, the mapping out of the conformation of the cardiac area and of the angle between cardiac and hepatic dullness are no less important than the accurate evaluation of auscultatory phenomena.

Changes in percussion findings may give early clews to dilatation of the heart and beginning decompensation. Alteration in outline may discover pericardial effusion. Weakening of the pulmonic second sound may forecast myocardial insufficiency and displacement of the heart lead to detection of a pleural exudate. Increase of cardiac dullness to the right may result from dilatation of the right heart, from pericardial effusion, or it may be evidence of a displacement of the heart due to pleural exudation or massive pulmonary consolidation on the left side. Apparent enlargement or displacement to the right may be the result of retraction of the right lung (Jurgensen).

As already noted, the heart rate is usually accelerated and the tachycardia may be moderate or marked. After crisis bradycardia may develop. Several instances of heart block developing in the course of the disease have been described.[38]

Cardiac arhythmias of all types may occur, especially in patients with old myocardial disease, endocarditis or atherosclerosis. They are always of serious portent except when they are allorhythmias that have been present for years without signs of cardiac disease.

Gallop rhythm, especially the protodiastolic variety—a three-time rhythm with the third sound occurring early in diastole—is occasionally heard and is usually indicative of myocardial weakness. Tic-tac rhythm or embryocardia occasionally occurs. The pulmonic second sound is usually markedly accentuated, probably as a result of the increased resistance, and therefore augmented pressure in the lesser circulation; and occasionally it is reduplicated. A loud snapping second pulmonic sound, other things being equal, is of good augury, and when this sound becomes enfeebled it may foretell failure of the right heart and collapse. Often one fails to recognize enfeeblement of this sound because of its increased transmission through consolidated lung tissue.

Heart murmurs are of common occurrence.[39] During the active febrile stage of the disease a soft blowing apical systolic murmur is usually audible. Unassociated with cardiac enlargement and localized to the apex, transmitted over the body of the heart but not usually lateralward, and disappearing during convalescence, such a bruit is to be considered a functional murmur and not indicative of a true mitral lesion. It may result from relaxation of the heart muscle, changed composition of the blood, or altered pressure in the pulmonic circulation. Of course if a preëxistent valvular lesion is present, the murmurs associated with it may be heard. Whenever murmurs appear during the course of an attack and especially if they are diastolic in time, the presence of an endocarditis should be suspected.

The development of arhythmia, gallop rhythm, embryocardia or of cardiac dilatation may come on gradually or abruptly, but outspoken evidence of cardiac weakness is uncommon before the third or fourth day of disease. Not infrequently it is detected just before or at the time of crisis—rarely after crisis. Cyanosis, dyspnea, chilliness, sweating, delirium, increased tachycardia and hypothermia are the signs noted in cases of syncope or collapse which may be fatal or from which recovery may follow. When such signs occur the outlook is always exceedingly grave, and this is especially true when they are of postcritical development.

Sudden death may result from acute dilatation of the heart or from pulmonary embolism.

The cardiac weakness is variously attributed to myocardial injury, the direct result of the toxemia; to increased cardiac strain, the result of obstructed pulmonary circulation; to the fever; to vasomotor paresis; or to a combination of these causes.

Newburgh and Porter [40] have shown that the heart muscle in pneumonia is essentially normal, having adjusted itself to its poisoned food as a result of a very gradual exposure to the toxin in the blood.

(*f*) *Skin.*—Herpes simplex occurs in from 5 to 50 per cent. of collected cases,[41] and by many is considered a favorable prognostic sign. The eruption appears most commonly on the lips or near the angle of the mouth, usually at the junction of the skin and mucous membrane; but it may develop within the nose, on the chin, ears, extremities and about the anal and genital regions. It may appear before the rigor or within the first few days of the disease, and rarely the vesicles may first erupt with beginning resolution. In some cases of herpes in the area innervated by the trigeminal nerve, Howard [42] found inflammatory and degenerative changes in the gasserian ganglion.

In an infectious disease of undetermined etiology the presence of facial, labial or nasal herpes brings into serious consideration lobar pneumonia, malarial fever, influenza and epidemic meningitis. Erythema of the face and of the skin of other parts of the body is often present during the febrile stage of the disease. Flushing of one cheek, on the same side as the pneumonia, is said to be of common occurrence.

Sweating may occur at any period of an attack, though it is uncommon except at crisis or with the development of complications. Occasionally at the height of the fever, instead of a hot, dry skin there is profuse perspiration (sudoral type). Accompanying defervescence there is usually a drenching sweat, especially marked in youthful patients. Profuse perspiration may appear in the preagonal stage of the disease with signs of collapse; as an accompaniment of the motor agitation of the delirious; and when empyema or other complications develop.

Miliaria crystallina and miliaria rubra quite often develop as a result of the sweating. Purpura and furunculosis are of uncommon occurrence, and a roseola-like eruption has been described. Jaundice is described under Complications (p. 50).

(*g*) *Gastro-intestinal Tract.*—As in most febrile diseases, gastrointestinal symptoms often occur without active disease of the digestive organs. The tongue is usually dry and heavily furred. Sordes may be present on the lips and teeth and anorexia is present from the onset. Nausea and vomiting are relatively infrequent symptoms except in children, in alcoholics, in patients with especially violent paroxysms of cough and in those with abdominal complications. In the cases collected by Norris, nausea occurred in 13.5 per cent., vomiting in 26.8 per cent.

Hiccough may be harassing and, when it cannot be relieved, clouds the prognosis. Persistent hiccough is often indicative of a diaphragmatic pleurisy or of peritonitis.

The bowels are usually constipated, sometimes regular and occasionally there is diarrhea. The last may be due to a purgative taken at the onset or to a complicating ileocolitis.

Tympanites or meteorism, especially common in the severe toxic cases and in those with grave circulatory disturbances, is an annoying and oftentimes an alarming symptom. All grades of abdominal distention are met with and, when an extreme degree is present, may interfere seriously with respiration. It may be due to a toxic paresis of the intestines, to enteritis, to limited mobility of the diaphragm, to derangement of the splanchnic circulation, or be associated with a complicating peritonitis. The occurrence of abdominal pain has been considered.

The liver is often enlarged in pneumonia, but the finding of a palpable liver edge may result not only from enlargement but may be due to displacement downward caused by the pressure of hepatized lung, pleural exudate or subphrenic abscess.

As in most infectious diseases, there is some enlargement of the spleen but it is not usually marked. The splenic dullness was increased in 90 per cent. of our cases but the border was palpable in only one-third of them. When the edge is felt it is usually soft and does not present more than a few cubic centimeters below the costal margin. With the subsidence of the acute stage of the disease the splenic swelling regresses.

Lymphadenitis with enlargement of the cervical and inguinal nodes has been noted often, but in the writer's experience it is a rare finding.

(*h*) *Nervous System.*—Nervous prodromata are uncommon, but next to the respiratory and circulatory symptoms the nervous manifestations are the most marked.

Headache is often present at onset and subsides during the progress of the disease. Rarely severe, it may be so intense as to suggest meningitis. The pain is usually increased by and may be excruciating during the paroxysms of cough.

Insomnia or restless sleep may occur early in the disease and may result from pain or from frequent coughing. Somnolence at onset is a sign of graver significance, except in children. Torpor and coma occur in the very toxic cases and with meningitis.

Convulsions are rare in adults, fairly frequent in children, and are not uncommon in the alcoholic, the epileptic, the insane and in individuals with a psychoneurotic tendency. Von Ziemssen has described recurring convulsions in children from the onset to the termination of an attack.

Delirium is the usual manifestation of the functional involvement of the nervous system. It is outspoken especially in children,[43] in the alcoholic, in the very toxic cases, in those with meningitis, in patients with apical pneumonia and in those with hyperpyrexia. Delirium occurs in from 15 to 31 per cent. of the cases. It is more commonly met with in the cases that go on to a fatal termination and in upper lobe consolidation. The delirium does not vary directly with the elevation of temperature.

The mental disturbances, often of abrupt onset, vary from a low muttering delirium to states of excitement, and outspoken mania has led to the admission of patients with acute pneumonia to insane asylums. There may be torpor, confusional states, disorientation—as to time, place or person—and general incoherence. Hallucinations, delusions of all varieties, paranoid ideas, etc., are not uncommon, and typical, expansive delirium with grandiose ideas occurs. During a delusional state the patient may do himself hurt or become suicidal.

Delirium tremens is often precipitated by an attack of pneumonia but is less often seen than when venesection was freely practiced. The delirium developing at the time of crisis, during crisis and postcritically, is an exhaustion psychoneurosis in contradistinction to the toxic types occurring in the course of the disease. Aufrecht has noted delirium after crisis in children and in adults who showed no nervous symptoms during the attack.

Postcritical delirium may develop immediately after crisis, with or without a marked fall of temperature, may reach its height in several days or a week, and may leave an altered mental state that requires weeks before returning to normal. In other cases a confusional state may occur that is corrected in a few days. (These phenomena are similar to those occurring after typhoid fever.)

Meningismus and meningitis are considered under Complications (p. 47).

Physical Findings.—DETERMINED BY INSPECTION.—Inspection yields data of great diagnostic worth. The rapid, shallow breathing, movement of the alæ nasæ, contraction of the accessory muscles of respiration, dyspnea, cyanosis of skin and mucous membranes, flushed cheeks and the presence perhaps of herpes labialis or herpes nasalis, are all suggestive.

The posture, too, may be helpful. When there is much thoracic pain due to accompanying pleuritis the patient often lies on the affected side and, by pressure with hand or pillow, aims to limit its motion. The dorsal decubitis is often assumed.

There is frequently limited expansion on the side of the diseased lung though the immobility is not so marked as when there is pleural effusion. When the lower lobe is involved, the upper thorax on the same side often has a wider excursion than does that on the healthy side. If the right lung is affected, compensatory over-expansion is sometimes noted on the left, and vice versa. It is not rare to see apparent lagging of the uninvolved side, a finding that may lead to an erroneous impression if noted early before other signs become manifest.

Limited movement of the diaphragm, as evidenced by altered Litten's sign, may be found.

The point of maximum cardiac impulse may be displaced slightly to the right when the left lung is involved and conversely.

Mensuration of the chest with cyrtometer or tape rarely yields any data of value. There may be increased fullness of the affected side when consolidation is outspoken.

Determined by Palpation.—By palpation we may discover or establish altered relative expansion of the two sides of the chest. Early in the disease there may be a diminution of vocal fremitus over the affected lung but more characteristic is the increased fremitus when consolidation has developed.

The vocal fremitus may be diminished if there is marked pleural thickening or if there is a very thick fibrinous pleural exudate. It is diminished or absent when there is pleural effusion and in so-called massive pneumonia when the bronchi are plugged with exudate. In such cases the fremitus may return, if through coughing the bronchial secretion is dislodged or evacuated. In women, children and in all individuals with a voice that is feeble or of high pitch, determination of altered vocal fremitus is of little value. In deep-seated or central pneumonia the fremitus may be unchanged.

A palpable friction rub may be found when fibrinous pleurisy is present and rhoncal fremitus is occasionally palpable when there is an accompanying bronchitis and during resolution.

Determined by Percussion and Auscultation.—Percussion and auscultation yield the most informing data.

(*a*) *Percussion.*—(i) *Stage of Engorgement.*—The normal pulmonary resonance is replaced by a note distinctly tympanitic in character. There is usually neither outspoken tympany nor outspoken dullness, but the note can be described best as a dull tympany. The cause of the hollow character of the sound is not completely established but it is likely due to diminished elasticity and relaxation of the lung, and, in part at least, to the transmission through the engorged tissue of the note from the trachea, bronchi and underlying relatively normal lung.

(ii) *Stage of Consolidation.*—The percussion note is dull. The area of dullness varies with the extent of the hepatization and is usually greater in size than is the consolidation itself. Recognition of the fact that the area of dullness may be localized and small will save errors in diagnosis, for it will lead to careful percussion of all areas of the chest. It is too common an error that, although the front and back of the chest are carefully explored, the axillary regions are often passed over unstudied. The error resulting may be maximum, for when consolidation begins in the upper lobes the dullness is often first to be detected in the posterior axillary line or at the apex of the axilla. Then, too, in women exploration of the middle lobe is often totally neglected because carelessness or mock modesty deters the examiner from raising a pendant breast. Failure to examine the entire chest thoroughly often proves embarrassing.

The note may be flat and a sense of increased resistance to the finger may suggest the presence of pleural effusion, though the absence of a board-like quality to the note and the accessory signs will save confusion. Lord [44] described the presence of a paravertebral area of relative resonance on the *affected* side in cases with extensive consolidation of a lower lobe, and this sign is often helpful in differential diagnosis.

A narrow zone of tympany at the upper level of dullness (Skoda's resonance) may be present, probably due to compression of the lung adjacent to the consolidated area. There is often a compensatory hyperresonance of the uninvolved portions of the lungs.

In central pneumonia the percussion note is often very slightly altered, sometimes entirely unchanged, and the diagnosis rests on the data furnished by the anamnesis, by inspection and auscultation.

(*b*) *Auscultation.*—Suppression of the breath sounds, partial or nearly complete, is often the first auscultatory finding in pneumonia. The discovery of diminished resonance, distant breath sounds and crepitant râles within a few hours of a rigor constitute strong presumptive evidence of a developing consolidation.

At first, the quality of the respiratory murmur may be practically unaltered, but as solidification of the lung progresses, expiration becomes lengthened, its pitch becomes higher and soon the breath sounds become more intense and outspokenly tubular in character. At the height of the disease they are shrill and high pitched during both inspiration and expiration. If pleural thickening is marked, if there is excessive fibrinous pleural exudation, if the bronchi are obstructed, distant tubular breathing may be present throughout the course. The altered character and intensity of the breath sounds is due to the ready transmission of the sounds in the trachea and bronchi through a solid conducting medium. The early suppression results from the incomplete infiltration of the lungs and the partial blocking of the bronchi and alveoli with increased secretion.

Of the adventitious sounds, the crepitant râle, as Laennec indicated, is the most important. He considered it "pathognomonic of inflammatory engorgement of the lung," and, though it is no longer so considered, it is suggestive and is met with only in early pneumonia, tuberculosis, atelectasis and infarct. Crepitant râles are very fine, crisp, metallic, consonating, dry sounds that are heard in showers toward the end of inspiration. They are only slightly altered by cough and may readily be confused with the fine râles heard in edema or congestion of the lungs, and in capillary bronchitis or with a pleural friction rub. They are produced by the inspiratory passage of air through tenacious secretion at the junction of bronchiole and alveolus in the neighborhood of consolidation.

This so-called "crepitatio indux" may come and go, and when consolidation is complete disappears. The fine râles accompanying resolution, "crepitatio redux," are often more moist in character. The appearance of crepitation in a new area of the lung is often indicative of the spread of consolidation. During the stage of resolution moist râles of all types and musical rhonci are heard, as the breath sounds lose their bronchial character and return to normal.

The transmission of the voice sounds is also altered. During the stage of engorgement it is often diminished, but when consolidation is complete it is increased. The spoken and whispered voice sounds are then loudly heard, more readily distinguished than over normal lung, and are high pitched and blowing in character (bronchophony). These findings are better noted in proportion as hepatization approaches the surface of the lung, and in deep-seated consolidation the intensity of the sounds is lessened but the altered qualities are still noted. The changed character and increased intensity of the voice sounds is due to the transmission through solidified lung parenchyma, which is an excellent conducting medium.

Bronchophony is more readily detected in men than in women or children, in the thin than in the obese. It may be absent in massive consolidation and is of lessened intensity or absent when there is pleural exudation. Occasionally the voice sounds have a nasal or bleating quality (egophony). The sound produced by cough also has a bronchial quality during the stage of consolidation.

The heart sounds are often transmitted loudly through the consolidated lung. In massive pneumonia other viscera may be displaced downward and towards the unaffected side.

Any or all of the foregoing signs may vary from day to day during the course of the disease, and during the stage of resolution a paroxysm of coughing may alter radically the auscultatory findings.

Resolution is usually detected first by the appearance of crepitation, the elements of which are coarser and more numerous than those of the crepitatio indux; the bronchial character of the respiratory murmur gradually becomes less well defined and with the diminishing dullness of the percussion note, coarse, moist and musical râles become more numerous, though not infrequently increasing resonance may develop without the occurrence of crepitant or coarse rhonci. The physical manifestations of consolidation do not disappear at the crisis and it is usual that impaired resonance, distant, altered breath sounds and râles persist for days after convalescence has set in. In cases with so-called delayed resolution or with organization of the exudate, the signs of consolidation may be present for weeks or months.

The signs of consolidation may be masked or absent when there is massive pneumonia, when there is obstruction of the bronchi, when pleural thickening or exudation is marked, and in central pneumonia. When the lower lobes are the site of disease the signs are usually first detected in the back near the hilus of the lung, and when the upper lobes are involved the signs may be discovered first near the apex of the axilla.

It is important to realize that deviations from the normal findings may be noted over the uninvolved lung. In extensive consolidation of one lower lobe, tubular breathing with or without râles may be heard near the spine on the opposite side, and occasionally the percussion note may be less resonant than normal. These findings may be due in part to compensatory overaction of the unaffected lung and to altered pulmonary circulation. Ignorance of these facts may lead to diagnostic errors.

Laboratory Findings.—BLOOD.—The red corpuscles are usually normal in number during the active stage of the disease. Instances of polycythemia have been recorded and it is not uncommon to find a moderate reduction of the number of red cells. After the crisis there is nearly always a decrease of 250,000 to 500,000 erythrocytes, and occasionally a moderate red-cell anemia develops. The cyanosis and the concentration of the blood during the febrile stage of pneumonia may be responsible for an apparent increase in the number of red corpuscles or may conceal the presence of a moderate anemia. According to Emerson, nucleated red cells, both normoblasts and megaloblasts, are more commonly found in pneumonia than in other acute fevers. The hemoglobin content is generally normal during the course, but with the crisis it usually shows a reduction more marked than that of the red cells leading to the blood picture of a mild or moderate secondary anemia.

The white corpuscles are increased from the onset and usually within a few hours of the initial chill leukocytosis is marked.[45-47] The count generally continues at a nearly constant level, with only slight increase or decrease, and does not show variations with the rise or fall of the temperature. An abrupt decrease in the number of leukocytes does not occur with defervescence at the time of the crisis, but their number falls more gradually and reaches normal from one to several days later. The diminution of the number of leukocytes may begin before, during or just after the crisis, and the continuance of a high count—especially if accompanied by a persistently high percentage of polymorphonuclear cells—suggests the presence of a complication, especially empyema or otitis media. A persistent leukocytosis with a diminishing percentage of polymorphonuclear cells and a proportional increase in the number of lymphocytes and eosinophils may indicate delayed resolution or, after serum treatment, serum sickness. In the cases with defervescence by lysis the decrease in the leukocytes is retarded.

Chatard,[48] in an analysis of 582 cases at the Johns Hopkins Hospital, found that more than half of the patients (350) had a leukocytosis of between 15,000 and 35,000, and nearly one-third (about 198) between 20,000 and 30,000. "The mortality is high when the leukocytes are below 10,000 per cu.mm., but steadily decreases and is lowest when the leukocytes are between 20,000 and 30,000. Between 30,000 and 60,000 the mortality is higher but remains at a fairly constant line: above 60,000, however, there is a decided rise in the mortality."

Analysis of 463 cases of pneumonia at the Hospital of the Rockefeller Institute and of 182 selected cases at the Minneapolis City Hospital[49] showed the same high mortality when the leukocytes were below 10,000 per cu.mm. and there was a similar progressive decrease in mortality with increasing leukocyte counts.

A leukocytosis of less than 10,000 per cu.mm. may indicate a very mild attack, a very severe infection with poor reaction, or the presence of a complicating infection, such as typhoid or malarial fever. The lowest count seen by the writer in lobar pneumonia was 900 leukocytes per cu.mm., and in this patient anatomical examination showed, in addition to the pulmonary condition, the intestinal lesions of typhoid fever. A persistently low leukocyte count is usually an unfavorable sign.

An average leukocytosis usually indicates a good reaction, and a gradual rise in the leukocyte count during the course of pneumonia is usually a favorable sign. A leukocyte count above 40,000 per cu.mm. may be of good omen but more often indicates the development of a complication. At best a very high count is a sign of doubtful prognostic value, for "it means that the patient is making a vigorous fight but gives no hint as to which will win, he or the infection."

The most marked leukocytic reactions are seen in males below the age of thirty and when there are complications.

(*a*) *Differential Count.*—The leukocytosis is generally due to a relative and an absolute increase in the number of the polymorphonuclear neutrophile cells. They average about 80 per cent. of the white corpuscles, though they may constitute 90 per cent. of them, and the lymphocytes vary inversely as the polymorphonuclear elements. The day before crisis there is often a rise in the number of cells and immature forms may appear in the circulation. During and after the crisis they diminish in number and continuing to fall after defervescence is established, may decline to a low level. The staining reactions and the condition of the leukocytes are said to be an indication of the condition of the patient, and predominance of degeneration forms, with poorly staining nuclei and cytoplasm, has been considered an unfavorable sign.

The eosinophils during the course of the disease are decreased or even absent, but after crisis they may rise to normal or even slightly above normal. Myelocytes are often present, especially after crisis, and may constitute as high as 12 per cent. of the white cells (Emerson). The large mononuclear and transitional cells show no constant variations. The platelets are often decreased during the course of an attack but are increased after the crisis.

The leukocyte count is of considerable diagnostic aid, especially in doubtful cases. The presence of leukocytosis helps exclude an uncomplicated typhoid or malarial fever, influenza and tuberculosis (except the miliary and meningeal types), and a leukocytosis in the aged or very young, with the evidence of an infection without localizing signs, should arouse the suspicion of a developing pneumonia.

(*b*) *Coagulation Time.*—The coagulation time in pneumonia has been the subject of much discussion. The formerly accepted view recently championed by Anders and Meeker,[50] that the coagulation time is shorter than normal during the active stage of the disease and returns to normal after the crisis, is no longer tenable. The observations of Dochez,[51] confirmed by Minot and Lee,[52] definitely establish the fact that the coagulation time is prolonged before the crisis and is normal after it.

The results obtained by Anders and Meeker and by others who report like findings have been explained by the fact that they employed the old clinical method of drawing blood through a puncture of the ear or finger. When blood is obtained thus, tissue juice is added to it and accelerates coagulation. True records of coagulation time, however, can be made only when no factors of clotting are introduced; and when blood is drawn by venapuncture this condition is met. When this method is used, a shortening of the coagulation time in pneumonia is never found, though a delay may be noted, especially in very ill patients. The shortening may be due to the increased circulating fibrinogen and the delay accounted for by an increase in antithrombin. The increased fibrinogen and antithrombin content of the blood is ascribed to changes in the liver induced by the action of the pneumococcus.

(*c*) *Oxygen Content of the Blood.*—In uncomplicated pneumonia the oxygen content of the peripheral venous blood is within normal limits and the differences noted in the febrile and afebrile periods do not exceed those found in health (Peabody[53]). There is no definite relation between either temperature or respiration and the oxygen content; except in the acute stage of the disease the normal oxygen level is associated with an accelerated respiratory rate. Because of tachypnea and perhaps because of a more rapid circulation, the organism compensates for the decreased respiratory surface due to pulmonary exudation. Occasionally, in uncomplicated pneumonia, a decreased oxygen content of the blood is associated with an increased carbon dioxid content, probably the result of an interference with the respiratory exchange of gases.

"In the terminal stage of the fatal cases of pneumonia in which death does not occur with great suddenness, there is often a progressive diminution in the oxygen content of the blood. Synchronous with this is a progressive decrease in the oxygen-combining capacity of the blood. These changes are usually seen in patients in whom an intense bacteriemia has developed and are analogous to those found in the arterial blood of infected rabbits, and to those resulting from the growth of the pneumococcus in blood *in vitro.* In all three conditions there is probably a change of oxyhemoglobin to methemoglobin. This change of the hemoglobin molecule, so that it no longer takes up and gives off oxygen readily, is probably a factor in the immediate cause of death in many cases of pneumonia." [53]

The carbon dioxid content of the blood is regularly diminished during the febrile period. In exceptional instances it may be normal or increased and it has been found so in association with low oxygen content of the venous blood. It tends to be lowest in the very severe cases and in the terminal stages of the disease, and is less altered in the mild and abortive cases. This diminution of the carbon dioxid content of the blood parallels other manifestations of metabolic disturbances and may be most marked after defervescence.[54] It bears no relation to the excretion of chlorids, but corresponds to the output of ammonia in the urine.

(*d*) ***Blood Cultures.***—Bacteriological studies of the blood in pneumonia give data of prime importance for accurate diagnosis and for serum treatment. The earlier reports on the incidence of bacteriemia in this disease record discordant findings, but more recent evidence demonstrates that the occurrence of a blood invasion is an index of a severe infection and a grave prognostic sign. The observations of Dochez [55] in 448 cases are typical. In 136 cases with positive blood cultures the mortality was 55.8 per cent., whereas in 312 cases with negative blood cultures the death rate was 8.3 per cent.

The type of pneumococcus present in the circulation is a determining factor in prognosis. Statistics show that, with the exception of infections due to Type I pneumococcus, in the treatment of which specific serum is efficacious, the more virulent the type of pneumococcus obtained from the blood, the less favorable is the outlook for recovery; and the greater the number of colonies that develop from 1.0 c.c. of blood, the graver is the prognosis. In brief, a pneumococcus bacteriemia is always a grave condition and the gravity of its significance varies directly with the number and the virulence of the circulating organisms.

Technic of Blood Culture.—Under aseptic conditions, from 15 to 20 c.c. of blood are obtained by venapuncture, usually from a vein in the antecubital fossa. The skin is most readily cleaned with tincture of iodin; the syringe is sterilized by boiling for fifteen minutes in a covered container, by heating in the autoclave or in a dry oven. A tourniquet, tightly applied proximal to the site of puncture, makes aspiration easier, and it is well to remember that oftentimes when a satisfactory vein is not visible, palpation may discover the presence of a suitable one. In the very obese it may be necessary to cut down upon a vein. When a puncture is unsuccessful, or when a hematoma is produced, it is well to withdraw the needle at once and to try another vein.

The blood obtained is immediately added to the culture media. It is the writer's practice to add 10 c.c. to a flask containing from 100 to 150 c.c. of glucose broth and to incubate it immediately. Varying amounts are added to tubes of agar melted and cooled to 45° C., and plates of the blood-agar mixture are made.

Growth in the broth is evidenced by diffuse turbidity. Growth on the blood-agar plates is shown by the development of colonies of pneumococci which appear as small dots surrounded by a green halo of methemoglobin. Organisms developing in the media are identified as pneumococci by the tests described under Bacteriology (pp. 4-8).

URINE.—The urine has the general characteristics noted in febrile diseases. It is scanty, of high color, increased specific gravity, contains a trace of albumin and often a few casts.

The output during the active period of the disease may be less than half the normal, but retention is not so common as in typhoid fever and anuria occurs only with a complicating nephritis. A postcritical diuresis is frequent. The deep color is due to increased excretion of urobilin and to concentration.

The urinary acidity, often increased during the febrile period, may be diminished after defervescence when the urine may be alkaline, perhaps due to absorption of alkali from the resolving exudate.[56] Palmer[57] has demonstrated the excretion of considerable quantities of an organic acid during the fastigium of many cases of pneumonia and Medigreceanu,[58] an increased output of glycuronic acid in the febrile period.

The urinary nitrogen is increased during resolution and more nitrogen is excreted than can be accounted for by the original quantity of exudate in the involved lung. A similar excessive excretion of nitrogen occurs in cases with delayed resolution and is evidence that this condition is one of continuing consolidation and resorption rather than one of retarded resolution.[59]

The diazo-reaction is often present but disappears with the onset of diuresis and is of no significance.

Albuminuria is generally present before crisis and may persist into convalescence. In Chatard's[60] series albumin was present in 77.6 per cent. of the cases; there was none in 16.8 per cent.; a faint trace in 16.2 per cent.; a trace in 68.8 per cent.; and a heavy trace in 15 per cent. There was an associated cylindruria in 25.2 per cent. of the cases. The albumin is usually present only as a trace. Deutero-albumose[61] and peptone[62] have also been demonstrated in the urine and acetone and diacetic acid are occasionally found.

The excretion of chlorids is partially or completely suppressed more often in pneumonia than in any other febrile disease. After crisis the output rapidly returns to normal. Chatard, in a study of the urine of 103 patients, found in 50.4 per cent. less than 1 gram per liter; in 31 per cent., less than 2 grams; in 12.6 per cent., less than 5 grams; in 3.8 per cent., less than 10 grams; and in 1.9 per cent., less than 15 grams. Complete suppression of chlorids is frequent.

The retention is often attributed to the storing of chlorids in the pneumonic exudate, but the experimental studies of Medigreceanu[63] and the clinical observations of Peabody[64] indicate this is only one factor and of itself incapable of causing so marked a retention. Peabody noted that though there is a storing of chlorin, sodium and calcium, potassium and magnesium are excreted normally or in excess; that during the period of retention the chlorin content of the blood is less than normal, and concluded that "since no organ or organs have been shown to store up large quantities of the retained substances it is probable that they are spread diffusely throughout the body." That this retention is not dependent upon a renal lesion is evidenced by the normal excretion of magnesium.

The loss of nitrogen and sulphur runs more or less parallel and is less marked in mild cases.[65] The relative desamidating capacity of the body is comparable to that in health, and the ability to oxidize the cystin group is normal or increased. During the febrile period creatinin is eliminated in excess, and during convalescence the output is less than normal. At the height of severe cases of pneumonia creatin may appear in the urine, to disappear during convalescence. In fatal cases it may be voided until death and may equal the creatinin in amount. During hyperpyrexia—especially in very toxic cases—large amounts of undetermined nitrogen may be excreted.

Dochez and Avery[66] have demonstrated in the urine of patients with pneumonia a specific soluble substance that gives a precipitin reaction with antipneumococcus serum corresponding in type to the organism with which the individual is infected. This substance has been found in the urine of more than half the patients studied. It may be detected as early as twelve hours after the initial chill; it may not appear until a later stage of the disease and, occasionally, it is excreted after recovery has occurred. Its persistence after convalescence may indicate delayed resolution. It is generally found when a pneumococcus sepsis exists, and the amount of precipitable substance in the urine seems to be an index of the severity of the disease. This specific precipitin test is of diagnostic and prognostic value, and since the type of pneumococcus responsible for a given infection can be determined by its utilization, it points the way for specific therapy.

SPUTUM.—*Sputum Cultures.*—Sputum cultures are of especial value in the study of lobar pneumonia when circumstances render the taking of a culture of the blood impracticable, or when blood cultures are sterile.

The isolation of the pneumococcus from sputum offers a rapid means of identifying the strain of the organism responsible for the infection. Care should be exercised to obtain a specimen from the deeper air passages and as free as possible from saliva. It is collected in a sterile container and sent at once to the laboratory for staining, culture and inoculation into mice.

In children from whom sputum cannot be obtained in the ordinary way, a curved sterile swab inserted into the pharynx will provoke a paroxysm of coughing and the sputum that is raised will often adhere to it, and from this cultures may be made.

DIAGNOSIS

The diagnosis of a typical case of lobar pneumonia is seldom difficult. The sudden onset of illness with a shaking rigor, fever, rapid shallow respiration and thoracic pain is suggestive. The presence of cough, tenacious rusty sputum, tachycardia, herpes and leukocytosis is corroborative evidence, and when, in addition to the foregoing, there are localized signs of pulmonary consolidation and suppression of the urinary chlorids the diagnosis is sure. Clinically, the disease has been established as lobar pneumonia, but the etiological diagnosis is not certain until the demonstration of the pneumococcus in blood cultures or sputum, or of the specific precipitable substance in the urine has been made.

Differential Diagnosis.—But lobar pneumonia may not always present so typical a picture, and it may tax diagnostic skill to differentiate it, promptly and certainly, from other conditions. In every case of fever of doubtful origin, repeated careful examinations of the lungs are indicated. This is especially true in childhood and in old age.

ACUTE TUBERCULOUS PNEUMONIA.—Acute tuberculous pneumonia may have as abrupt an onset as lobar pneumonia, and may be characterized by all the signs enumerated above, but the history of intimate exposure to tuberculosis—especially in childhood—of an idiopathic pleurisy or of hemoptysis, chronic cough, easy fatigability and loss of weight, the presence of old tuberculous infection of the glands, etc., may suggest the correct diagnosis. When these features are lacking, an irregularly remittent or intermittent fever, failure to defervesce within the ordinarily expected time, and especially when the consolidation is localized in an apex or in an upper lobe, are very suggestive. Further, in tuberculous pneumonia the constitutional symptoms are often less marked, hemoptysis is more common, the sputum less viscid and more purulent, leukocytosis less striking, cyanosis more intense and emaciation more rapid. Finally, careful and repeated examinations will often demonstrate the presence of tubercle bacilli in the sputum.

BRONCHOPNEUMONIA.—Bronchopneumonia may cause confusion when it leads to pseudo-lobar consolidation of the lung and at times differential diagnosis may be impossible. The greater frequency of lobular consolidation in infants and in the aged, its more common occurrence as a complication of or sequel to other diseases, its insidious onset, more circumscribed distribution and the greater incidence of termination by lysis are differential points.

PLEURAL EFFUSIONS.—Pleural effusions may be mistaken for lobar pneumonia and vice versa. The limited expansion, the displacement of other viscera, the diminution or absence of vocal fremitus, the boardlike flatness on percussion and the suppression of respiratory murmur and voice sounds, even the paravertebral triangle of dullness on the unaffected side, may be found in massive pneumonia. On the other hand, the compression of lung tissue adjacent to pleural effusions may give the signs of consolidation.

The history of a gradual onset of symptoms, the absence of a chill and of blood-stained sputum speak in favor of effusion in equivocal cases, and the demonstration of displacement of the heart to the unaffected side, of wooden flatness and Grocco's triangle on percussion, suppressed breathing and absence of râles on auscultation are points against the diagnosis of pneumonia. It cannot be too strongly emphasized that whenever doubt exists as to the presence of a pleural effusion exploratory paracentesis of the thorax is urgently indicated. A syringe and needle suitable for thoracic tapping should be part of the equipment of every good clinician. Further, a roentgenogram gives decisive differential data.

INTERLOBAR EMPYEMA.—This condition may give all the signs of consolidation of lung tissue and may be confused with pneumonia, delayed resolution and tuberculosis. The reappearance of fever after defervescence, of sweats, chilliness, anemia, prostration and the development of clubbed fingers and leukocytosis usually point the way to a correct conclusion, or exploratory paracentesis or roentgenoscopy may discover the condition.

INFARCTION OF THE LUNG.—Infarction of the lung may closely simulate lobar pneumonia. The history may be identical and but for the detection of conditions that may lead to embolism, differentiation may be impossible. The sudden onset of thoracic pain, cough with bloody sputum, dyspnea, cyanosis, fever, etc., point rather to infarction when they develop in patients with acute or chronic endocarditis, peripheral thrombosis, sepsis of puerperal or of other origin, sinus thrombosis, following crushing injuries, etc. In infarction, chill, rapid rise of fever and defervescence by crisis are less common than in pneumonia, and the sputum contains bright red blood and fewer bacteria. Blood and sputum cultures are helpful diagnostic aids in doubtful cases.

ATELECTASIS.—Atelectasis may present signs difficult to differentiate from those of pneumonia, though the dullness due to it is less constantly associated with intense tubular respiration; and further, the percussion changes are modified and may even approach normal, following a number of deep inspiratory efforts.

NON-TUBERCULOUS BASAL INFECTIONS.—These offer little difficulty and are differentiated from lobar pneumonia by the history, mode of onset, slight constitutional symptoms, purulent sputum and protracted course.

OTHER DISEASES OF THE PLEURA AND LUNGS are rarely difficult to exclude. Tumors of the pleura, tumors and cysts of the lung, and chronic passive congestion of the lungs occasionally present signs similar to those due to pneumonic consolidation, but the history and accessory diagnostic aids will usually establish their true nature.

Central pneumonia may be overlooked for several days.

TYPHOID FEVER.—Pneumonia should rarely be confused with typhoid fever, though occasionally some difficulty may arise. The history of sudden onset with chill and thoracic pain, the presence of herpes, tachycardia, and especially of accelerated, shallow respiration, the leukocytosis and the suppression of the urinary chlorids exclude typhoid fever even before signs of consolidation of the lung develop.

INFLUENZA.—Influenza can usually be excluded by a history of exposure to contagion, by the greater prostration, green sputum, different course and by the results of laboratory investigation.

Meningitis.—Meningitis may be wrongly diagnosed in uncomplicated pneumonia attended at onset by marked cerebral symptoms or when there is meningismus, and examination of the spinal fluid may be the only means of differentiation. This is especially true in childhood, and in adults in whom the development of the signs of pulmonary consolidation are delayed.

Acute Abdominal Diseases.—Reference has already been made to the difficulties of diagnosis that may arise when acute abdominal pain is a striking feature at the onset or early in the course of pneumonia. The character of the pain, its localization, its association with rigidity of the abdominal muscles, distention of the abdomen, nausea, vomiting, fever, and leukocytosis may give rise to the suspicion of peritonitis. Acute appendicitis, perforated gastric ulcer, intestinal perforation, cholecystitis, pancreatitis, even pelvic inflammatory disease may be closely simulated. Differential diagnosis rests upon careful examination of the thorax, laboratory studies and the detection of true spasm of the abdominal muscles no less than upon an accurate knowledge of the symptoms and signs of disease of the abdominal viscera, vessels and serous lining.

X-ray Examination.—As an accessory to the ordinary methods of physical diagnosis and occasionally as the direct means of establishing the presence of a suspected but undiscovered pneumonic consolidation the *x*-ray is of great value. Roentgenography is more useful than fluoroscopy in so far as it gives a permanent record and the opportunity to study the evolution of a given lesion. By means of the *x*-ray the exact location and extent of the inflammation can be determined and the development of effusion in the pleural sacs may be disclosed before it is of sufficient size to give diagnostic signs.

The shadow cast by pneumonic consolidation is less dense than that caused by pleural exudation or by neoplasm of the pleura or lung, and it is less uniform. As a rule, in the depth of the shadow, or more usually near its periphery, there is a diffuse, uneven mottling and the margins of the shadow are irregular, hazy and ill-defined. Roentgenographic studies[67] indicate that the consolidation in lobar pneumonia begins as a conical or triangular area of solidification with its base near the pleural surface of the lung and spreads towards the hilus. Often the infiltration does not reach the hilus and this may explain the absence of tubular breathing and bronchophony in some cases, as a central localization of the lesion may in others.

The onset of resolution can often be detected roentgenographically before the clinical course or physical signs give evidence of its occurrence and the *x*-ray has shown that resolution usually starts in the depth of the exudate, spreading irregularly from one or several points near the hilus of the lung towards the periphery. Marked changes in the shadow may occur within the course of a day and the picture of a normal lung may not be obtained until some time after convalescence has been established.

Pleural effusion is distinguished roentgenographically from pneumonia by the following differences: the shadow is denser and more uniform; its outlines are more sharply defined and the upper limit is often curved; depression of the diaphragm, displacement of the cardiovascular stripe and a basal localization with obliteration of the complemental space are more often seen in the plates of pleural effusion.

In encapsulated exudates and when the collection is interlobar the uniform dense shadow, its clearly demarcated borders and anatomic position are diagnostic.

The *x*-ray findings in thickened pleura are often confusing, but the uniform hazing without mottling and the more even paling of the shadow at its borders help to differentiate them from those in lobar pneumonia.

COMPLICATIONS

Respiratory System—PLEURISY is so usual an occurrence in the course of lobar pneumonia that it can scarcely be termed a complication. In practically every case in which the consolidation reaches the periphery of the lung a fibrinous pleurisy develops. Occasionally, the plastic exudate is of unusual thickness and extent, modifying the physical signs of the consolidation and leading subsequently to the development of adhesions. Though generally limited in area to the site of the pneumonia, it may be more extensive and occasionally occurs on the uninvolved side with resultant difficulty in diagnosis. Signs of plastic pleurisy were found in the series reported by Chatard in 51.2 per cent., but the incidence is undoubtedly greater than this figure indicates.

The presence of fibrinous pleurisy is evidenced by characteristic thoracic pain, limited mobility of the affected side and by the presence of a friction rub. The last may be transitory and is readily confused with intrapulmonary crepitation. It is a point of practical importance that the sudden disappearance of pleural pain and pleural friction may indicate the accumulation of fluid as well as a subsidence of pleuritis.

Small serous effusions are of common occurrence and were found by Lord [68] in 37 per cent. of 154 autopsies. Serous effusions sufficiently large to be detected clinically, i.e., 400 c.c. or more, are rare.

EMPYEMA must be looked upon as a possible complication in every case of lobar pneumonia. Musser and Norris [69] found it in 2.2 per cent. of 13,550 clinical cases and in 5.1 per cent. of 973 autopsies. McCrae [70] found it in 3.6 per cent. of 805 cases at the Johns Hopkins Hospital. The incidence of empyema as a complication varies greatly from year to year. It is common in childhood, occurs more frequently in the negro than in the white race, and is slightly more frequent in cases of pneumonia following trauma of the chest wall.

Empyema is a complication rather than a sequel of pneumonia, as evidenced by the persistence of the fever after the pneumonia has cleared, and by its occurrence during the active stage of the disease. It is more common after a severe attack and especially when more than one lobe is diseased. Its presence is usually first manifest during the stage of resolution.

The organism responsible for its production is either the pneumococcus or the *Streptococcus hæmolyticus.* According to Ewart, in children empyema is due to the pneumococcus in 75 per cent. and to *Streptococcus hæmolyticus* in 25 per cent., whereas in adults the reverse is true. In the series of 22 cases collected by McCrae,[71] the former was found in 20, the latter in 2. In the pus of empyema cases Lord found the pneumococcus in 39.4 per cent., the streptococcus in 20.4 per cent., staphylococci in 3.6 per cent., mixed infections in 16 per cent., and in 18.2 per cent. the cultures were sterile. Failure to obtain bacterial growth in cultures of the pus of empyema may indicate that the causal organism has died or that the exudate is tuberculous.

The mode of onset of empyema cannot be accurately studied, as it may be masked by the symptoms of the pneumonia. In parapneumonic empyema [72] the only signs may be increased dullness on percussion, an increased leukocytosis and sweats. In metapneumonic empyema, which is far the more common type, the most suggestive symptom is the persistence of fever. In McCrae's series of 29 cases, in 21, after the pneumonia had subsided, the temperature did not become normal; it reached normal for a brief interval in 4 cases, remained normal for less than twenty-four hours in 2 cases, for twenty-four hours in 1 case, and for three days in 1 case. The fever during the course of the empyema, though usually very irregular and often intermittent, at times may be continuous. The pulse is rapid and tachycardia may be the most striking clinical symptom. In a small percentage of the cases the rate is normal or only slightly increased.

The respirations are more constantly increased in frequency, varying between 20 and 36 per minute, are shallow and often labored.

Cyanosis may be present, but more characteristically there is progressively increasing pallor with a sallow tint to the skin. Sweats and occasionally chills, rapid loss of weight and discomfort due to pain or dyspnea are usual. Clubbing of the fingers and toes may develop rapidly.

There is an outspoken leukocytosis of the polymorphonuclear variety more marked than during the course of the pneumonia, and averaging between 20,000 and 30,000. The development or reappearance of such a leukocytosis after a critical defervescence is a very suggestive sign.

The physical signs are those of a pleural effusion. *Inspection* is of little aid in diagnosis. The limited expansion of the involved side may be interpreted as due to the pneumonic process itself, and bulging of the interspaces should not be waited for. *Palpation with auscultation* gives the most helpful data. The vocal fremitus, classically absent when there is fluid in the pleural sac, may be retained in metapneumonic empyema, perhaps due to the presence of consolidated lung tissue behind the exudate, perhaps as a result of the tension of the exudate itself. In some instances the absence of vocal fremitus may decide in favor of pleural exudation and against pulmonary consolidation. *Percussion* may show very little change from that noted during the pneumonia, but more often the note is duller and characteristically it is flat. The complete absence of resonance due to pleural exudation is associated with a sense of wooden resistance to the pleximeter finger, so typical that it warrants exploration, even when it is the only suggestive sign of fluid. A band of Skodaic tympany may be present at the upper level of flatness, but dullness shifting with change of posture has never been seen by the writer in empyema without pneumothorax. Occasionally, the anterior limit of altered percussion note is determined as a sharp vertical line in the axilla (encapsulated empyema). In interlobar empyema the signs may be outlined along the course of the lung fissures. *Auscultation* discloses marked changes in the breath sounds and in the transmission of the voice. The respiratory murmur may be completely suppressed or more often it may be faintly heard, usually with a distinctly tubular modification. The change in the breath sounds over closely adjoining areas may be suggestive. The voice sounds are characteristically altered above the level of the fluid and generally have a curious high-pitched nasal quality that is difficult to describe (egophony).

The early recognition of an empyema is of maximum importance, for the outlook is good when a prompt diagnosis is made and efficient treatment is instituted early. Recognition of the fact that no physical sign is constantly present, and the willingness to explore the chest with an aspirating needle whenever the symptoms and some of the signs are noted will save many a life and lead to restoration of the function of many a lung.

The prognosis of empyema is about the same as that of pneumonia itself. Pericarditis and endocarditis occur more often when empyema develops than in uncomplicated pneumonia.

The exudate is generally odorless, thick, creamy pus consisting mainly of polymorphonuclear leukocytes. Mononuclear and endothelial cells are present in relatively small numbers. Pneumococci living and dead may be found both intracellularly and extracellularly.

The empyema may rupture into the lung, a bronchus, the pericardium or, exceptionally, through the thoracic wall. Very rarely aspiration may be followed by absorption of the exudate, but as a rule thoracotomy with resection of one or more ribs is necessary.

The diagnosis of the rupture of empyema into a bronchus is suggested whenever, after a pneumonia, the patient suddenly expectorates a large quantity of purulent material and at the same time his symptoms lessen or disappear, the physical signs become less abnormal, the fever falls and the leukocytes diminish in number.

Encapsulated interlobar empyema may escape detection or be discovered with great difficulty. Whenever there is persistent fever, tachycardia and leukocytosis following an attack of pneumonia, especially if there are also pallor and sweats, the condition should be suspected even though physical signs do not indicate a pleural exudation. Repeated needling of the chest along the line of the interlobar fissures of the diseased side may establish the diagnosis or it may be located by the use of the x-ray (q.v.).

Encapsulated interlobar empyema may rupture into a bronchus and a localized pyopneumothorax may result. The writer has seen one such case in which the suspicion of its occurrence was strengthened by the demonstration of flatness that shifted along the line of the fissure with change in position.

PNEUMOTHORAX is a very rare occurrence and has been noted most often when an empyema has ruptured into a bronchus.

BRONCHITIS is extremely common at onset and may last throughout an attack. Purulent or membranous tracheitis is a rare event.

EPISTAXIS may occur as the initial symptom of pneumonia and may recur from time to time throughout the course of the disease. It is usually of no moment except in the aged or when it is a manifestation of a hemorrhagic tendency in the cases of pneumococcus septicemia.

LARYNGITIS may be present before or occur during pneumonia. Edema of the larynx and suppurative perichondritis of the larynx occur, but fortunately they are very rare.

ABSCESS OF THE LUNG is an infrequent complication. It was noted clinically in 76 of the 12,030 cases collected by Musser and Norris, and in 9 of 658 cases analyzed by McCrae at the Johns Hopkins Hospital. Lobar pneumonia is the most frequent single cause of abscess of the lung, and in 50 cases at the Massachusetts General Hospital 14 cases could be attributed to it.

There may be a single large abscess but multiple small ones occur more commonly. The abscesses generally form near the periphery of the lung, are irregular in contour and may have a limiting membrane, though more often the boundary is indefinite and consists of necrotic tissue. The contents may be evacuated through a bronchus or the abscess may rupture into the pleura, pericardium or the esophagus.

Clinically, abscess is often confused with empyema and delayed resolution. Its onset is insidious, its course not characteristic.

Irregular protracted fever, sometimes with chills, persistent leukocytosis and pallor, loss of weight, cough that is moderately productive or that may lead suddenly to the expectoration of a large quantity of purulent secretion are the classical symptoms. The cough and expectoration may be influenced much by change in posture. The physical signs are those of consolidation, and after a large quantity of sputum has been raised the signs of cavity may be detected. The sputum, first tenacious, then mucopurulent, later purulent, varies in quantity up to several hundred cubic centimeters daily. Yellow or greenish at first, it is later often blood-containing, and sometimes foul. After standing it separates into three layers. Microscopically, pus cells, detritus, epithelial cells, crystals and more characteristically, particles or masses of lung tissue and elastic fibers are found.

After an attack of pneumonia, exacerbation of fever with leukocytosis, absence of the signs of resolution and the expectoration of large amounts of purulent sputum suggest an empyema that has ruptured into a bronchus or a pulmonary abscess. Frequently examination of the sputum will differentiate between them or recourse must be had to the *x*-ray.

GANGRENE OF THE LUNG is a rare sequel of pneumonia and is most common in the aged. It may begin in a pulmonary abscess or start in an old tuberculous lesion. It was found in 0.49 per cent. of 27,761 cases collected by Musser and Norris and, together with pulmonary abscess, in 0.4 per cent. of 500 cases studied by Lord. Like abscess, gangrene is often overlooked clinically. The symptoms and signs closely resemble those of abscess but the constitutional symptoms are more marked and the sputum more foul. The latter is generally outspokenly fetid. It is thin, brownish, often chocolate-colored, due to altered blood. Microscopically few red corpuscles are found. Elastic tissue is less abundant and Dittrich's plugs are more abundant than in the sputum from abscess.

Gangrene of the lung may lead to the development of empyema or pyopneumothorax and to the formation of cavity. Death from abscess or gangrene of the lung may result from intoxication, suffocation, collapse or cerebral abscess.

DELAYED RESOLUTION.—The clearing of the exudate in pneumonia is brought about through a process of autolysis. Some of the exudate is removed by expectoration but the major portion of it undergoes digestion by autolytic enzymes liberated by the leukocytes. In a variable period of time resolution is complete, and often within a week or two the physical signs of consolidation have disappeared and clinically the lung is restored to its normal state.

In some cases resolution may not proceed in this way, but its onset is delayed or its course is protracted.[73] Delayed resolution occurs in from 3 to 5 per cent. of all cases.[74] It occurs more often in men than in women, in negroes than in whites, in pneumonia of the lower lobes, in the aged, the debilitated and in alcoholics. In the latter it may cause death from gradual or sudden cardiac failure.

Signs of consolidation may persist as long as ten or twelve weeks and yet the lung may clear.

A febrile crisis may occur and the subjective symptoms subside, but the local signs of consolidation persist, to regress very gradually over a period of days or weeks. There may be a lysis and gradual subsidence of symptoms but consolidation of the lung associated with irregular fever and sweats may persist. Finally, the fever may remain elevated, and the symptoms and signs fail to disappear, until the patient dies from exhaustion.

The condition is most often confused with pulmonary tuberculosis, interlobar empyema, pleural effusion and pulmonary abscess.

SUBPHRENIC ABSCESS is a very rare complication and deserves mention mainly because it is apt to be confused with empyema. It is probably the result of infection by direct extension through the diaphragm and not a metastatic process.

MEDIASTINITIS AND BRONCHIAL LYMPH GLANDS SUFFICIENTLY ENLARGED TO CAUSE SYMPTOMS OF PRESSURE have been described in pneumonia. Both are extremely rare happenings and of little clinical interest.

Cardiovascular System.—The cardiac complications of pneumonia are of cardinal importance, not alone because of their influence on the immediate prognosis but because of the permanent changes they may cause.

PERICARDITIS is the most frequent cardiac complication of pneumonia and occurs more often than bedside observations indicate. Collected statistics show a clinical incidence of 1.5-2.5 per cent., whereas according to postmortem studies it is found in 10 to 15 per cent. of the fatal cases. It develops most commonly in young adults and is not rare in terminal pneumonia.

Pericarditis develops at the height of the disease, and because of its insidious onset is usually not detected. Because of the frequency with which it occurs when there is consolidation of the left lung it has been thought the result of infection by direct extension; but the studies of Chatard,[75] of Sears and Larrabee,[76] and others indicate it is generally of metastatic origin. The incidence varies with different epidemics. Usually of the fibrinous type, effusion occasionally develops but it is rarely of sufficient size to require paracentesis. Purulent pericarditis demands prompt surgical intervention.

The diagnosis may be suggested by increasing cyanosis, dyspnea and tachycardia and is confirmed by the detection of a pericardial friction rub or when, less often, effusion occurs, by the appearance of the signs of fluid in the pericardial sac. Recognition of a pericardial friction rub may be difficult, due to the presence of intrapulmonary sounds or of a pleuropericardial rub. It is essential to listen daily over the sternum, along the sternal margin and over the precordium in every case of pneumonia, or the presence of a pericardial rub may escape recognition.

The prognosis when pericarditis develops is exceedingly grave, in part because of the condition itself, in part because of the frequently coincident sepsis or myocarditis. The existence of the complication is so often overlooked that accurate mortality statistics are not available. Of the cases recognized clinically, from 50 to 80 per cent. end fatally.

ENDOCARDITIS also is undoubtedly much more frequent than clinical statistics indicate.[77-79] This is illustrated by a comparison of the figures obtained from the clinical and pathological records analyzed by Musser and Norris, who noted a clinical incidence of 0.44 per cent. as contrasted with the finding of anatomical lesions in 5.8 per cent. It is said to occur more often in patients over 30 years of age, more often in women than in men, and especially frequently in those with preëxistent valvular disease.

In the majority of cases it is of the ulcerative type. Though the left heart is involved more often than the right, the right heart is attacked more often in pneumococcus infections than in most other varieties of endocarditis. According to Netter's figures, in 6.7 per cent. of other types of endocarditis the right side of the heart is affected, whereas in 17.8 per cent. of the cases of pneumococcus endocarditis it is diseased. The aortic and pulmonary valves are the ones most often involved and whenever the former are implicated, with rare exceptions, the lesion is ulcerative.

As a rule, characteristic physical signs are lacking and the involvement of the heart is first discovered at autopsy. In some cases the subjective manifestations indicate the condition, especially when the symptoms are those of infarction. When there is infarction of the lungs, thoracic pain, bloody sputum and signs of pulmonary consolidation may be found; in infarction of the spleen, there is pain in the lower left axilla or left hypochondrium, enlargement and tenderness of the spleen; in infarction of the kidneys, lumbar pain, oliguria and hematuria may be found; and in infarction of the central nervous system there is meningitis, hemiplegia, etc.

The existence of endocarditis is to be suspected in every case of pneumococcus sepsis (q.v.). Its occurrence is to be considered whenever, in a prolonged attack of pneumonia, typhoidal or meningeal symptoms develop and whenever, after the temperature has fallen to normal, there is a return of an irregular fever.[80]

The character of the physical signs may be diagnostic. The detection of a systolic murmur is of little help, for it occurs regularly in lobar pneumonia without endocardial involvement. The marked alteration in the character of a systolic murmur, especially when it takes on a musical quality, is suggestive. A diastolic murmur usually is indicative of endocarditis.

In most cases the fever is irregular, sometimes intermittent and associated with recurrent chills, leukocytosis, rapidly increasing secondary anemia, and oftentimes the development of transitory nodular erythema and purpura. Meningitis complicates endocarditis in over 50 per cent. of the cases.

The prognosis is extremely grave. Of the cases diagnosed very few recover. If death does not occur, chronic valvular disease results.

Myocarditis is not a usual complication of pneumonia, though myocardial weakness is an occurrence of varying frequency and there is often evidence of embarrassment of the heart muscle due to the altered pressure in the pulmonary circulation or dependent upon the existent toxemia.

Permanent injury of the myocardium due to pneumonia is a very rare event.

Tachycardia and the various types of arhythmia that may occur have been considered.

Peripheral venous thrombosis is uncommon in pneumonia and has been found in about 0.5 per cent. of a large series of cases.[81] The rarity of it is curious, when one recalls how rich pneumonic blood is in the elements necessary for coagulation. It is a sequel rather than a complication, the majority of the reported cases occurring during convalescence. The veins of the lower extremities are most often involved and, as in thrombosis of the femoral veins due to other infectious diseases, the left side is more often affected. It has been observed also in the veins of the upper extremities, the external jugular, the superior longitudinal sinus and the cerebral veins. Thrombosis is slightly more common in protracted pneumonia, and in men than in women. Arteriosclerosis, feeble circulation and an altered condition of the blood are predisposing factors, but the immediate cause is probably an infective phlebitis. The symptoms do not differ from those due to thrombophlebitis of different etiology, and gangrene may result.

The prognosis differs, depending upon the vein affected. The outlook when the femoral vein is involved is good. Pulmonary thrombosis may cause sudden death.

EMBOLISM OF THE ARTERIES is very rare, but EMBOLISM OF THE ABDOMINAL AORTA, of the lenticulo-optic artery and of the popliteal artery have been described.

The emboli may be of venous or of cardiac origin.

Urinary System.—The transitory albuminuria and cylindruria of the active febrile stage of pneumonia and their causal renal irritation are to be regarded as regular features of the disease. Frothingham's studies[82] of a small series of cases of this type showed no impairment of renal function.

It is often difficult to distinguish between signs of no import and those indicative of true renal degeneration or inflammation. Definite nephritis, however, is rare and occurs as a complication in less than 1.0 per cent. of the cases. It may develop at any time in the course of an attack. Acute glomerulonephritis may occur. Edema is uncommon, hemoglobinuria is exceedingly rare, but hematuria is more frequently met. Pneumonia is not a common cause of nephritis and the renal disorders due to it are usually either rapidly fatal or end in complete recovery.

Genital System.—Suppurative orchitis following pneumonia has been recorded.

Skin.—Herpes simplex, erythema and sudamina (miliaria crystallina and rubra) are among the ordinary findings in pneumonia.

In the septicemic cases, purpura, erythema multiforme and erythema nodosum occur. Furunculosis may develop and erysipelas and pemphigus may be accidental occurrences. Metastatic pneumococcic dermatitis and postpneumonic symmetrical gangrene have been described. Herpes zoster is a rare complication, but the writer has seen it twice in the epidemic of 1917, both times in elderly women during convalescence from a mild attack.

Nervous System.—The frequency and the varieties of DELIRIUM occurring in pneumonia have already been considered. Other nervous symptoms undoubtedly due to toxemia and not dependent upon anatomical lesions may occur.[83] COMA and STUPOR sometimes associated with vomiting, HEADACHE and SIGNS OF MENINGEAL IRRITATION are unfavorable symptoms that may appear without the development of a true meningitis in

children, alcoholics, in very toxic cases and in association with otitis media.

PSYCHOMOTOR AGITATION in the neurotic or very toxic cases may lead to such physical activity as to embarrass an already laboring heart.

MENINGITIS occurs in less than one per cent. of all cases of pneumonia. It is most frequent in children under ten years of age and is almost uniformly fatal.[84] Meningeal symptoms may precede the signs of pneumonia or they may develop after the signs of pneumonia have subsided.[85] The infection of the meninges may be hematogenous, otogenous, lymphogenous or perhaps by direct extension from the paranasal sinuses. Probably in the majority of cases it is a metastatic infection of hematogenous origin and its development in only a small group of those with bacteriemia may be due to the existence in these of altered conditions of the thecal circulation. Anatomically the lesion is a purulent meningitis, indistinguishable from that due to the meningococcus or the influenza bacillus with the exudate widely distributed over the brain and spinal cord.

The symptoms may be completely masked by the toxic nervous symptoms of pneumonia and may be completely simulated by those of meningismus. Headache, photophobia, vomiting and constipation are suggestive. Stiffness of the neck, retraction of the head and Kernig's sign are even more so, and the occurrence of paresis or paralysis of the cranial nerves, convulsions, opisthotonus, emprosthotonus, hyperesthesia, choked disk, Kernig's, Babinski's and Brudzinski's signs are practically diagnostic. The conclusive evidence of meningitis is furnished by lumbar puncture. The spinal fluid obtained is turbid or purulent. It is often under increased pressure, shows an increased content of protein, contains many leukocytes—chiefly of the polymorphonuclear variety—and many pneumococci. Purulent meningitis may develop weeks after recovery from pneumonia.

It is important to recall that though many of the foregoing symptoms may be present and the clinical syndrome be indistinguishable from meningitis, spinal puncture may show a normal fluid or autopsy may show no anatomical changes in the central nervous system. This condition is termed *meningismus.* It occurs in the very toxic pneumonias, especially in the neurotic and in children, and is of no prognostic moment.

MENINGO-ENCEPHALITIS with signs of localized or focal cerebral disease has been reported.[86, 87] The condition is of very rare occurrence, has a bad prognosis and is manifested by the signs of increased intracranial pressure and the development of hemiplegia, monoplegia, or by disturbances of the cranial nerves. The pathology of this complication is not thoroughly established. Tetany, transitory loss of the pupillary light reflex[88] and temporary diminution or loss of the knee-jerk have been seen during the course of the disease.

PERIPHERAL NEURITIS, PARESIS OR PARALYSIS OF THE VARIOUS CRANIAL NERVES have been noted during pneumonia or in the convalescence from an attack. These symptoms are of toxic origin and recovery from them without residual symptoms is the rule. They have no influence on the general prognosis.

HEMIPLEGIA [89] is a rare complication that may result from cerebral thrombosis, embolism or abscess. There is another type of pneumonic hemiplegia occurring in young, vigorous people and having a better prognosis. This type, without gross anatomic lesion, appears within the first few days of the pneumonia or may precede it, and often before the development of paralysis there are ataxic aphasia, headache, syncope, vertigo, mental confusion and paresthesia of the side later paralyzed. This type of hemiplegia is of uncertain etiology and is variously ascribed to hysteria, encephalitis, meningitis and to cerebral ischemia due to insufficient circulation.

Organs of Special Sense.—OCULAR COMPLICATIONS are rarely seen. Instances of conjunctivitis, ulcerative keratitis and abscess of the cornea occur, and panophthalmitis and hemorrhagic retinitis of embolic origin have been described.

OTITIS MEDIA is most often met with in childhood. It occurs in about 3 per cent. of the cases of pneumonia of children and in less than 1 per cent. of those occurring in adults. The ear may become infected by extension from the throat or nasopharynx or through the blood stream. The process generally leads to suppuration and the symptoms generally are those of a purulent otitis media. Occasionally, the clinical picture closely simulates a meningitis. Mastoiditis, sinus thrombosis or meningitis may follow by extension. If paracentesis is not done, perforation of the tympanum results often with a consequent chronic discharging otitis, but the hearing is rarely impaired. The possible evil consequences of middle-ear disease can usually be avoided by frequent careful examinations of the ear in all pneumonic children and in all patients with signs of meningitis or with symptoms of otitis.

Thrombosis of the cerebral sinuses is to be suspected whenever, during or after an otitis media, cultures of the blood previously negative, yield pneumococci (Libman and Celler [90]).

Muscular System.—ARTHRITIS [91-94] is a very unusual complication, developing in less than 0.5 per cent. of the cases. It may occur at any stage of the disease, most often in the second week and, like other manifestations of sepsis, it occurs most often in children. Mono-articular or polyarticular, it shows a tendency to involve the large joints, especially the knees, and there may be synovitis or bursitis independent of or associated with the arthritis.

Mild cases with joint pain, tenderness, redness and slight swelling are probably often overlooked and subside spontaneously. Cases with moderate serous effusions occur with little constitutional disturbance. More severe cases suffer severe arthralgia, show marked signs of arthritis and develop purulent exudate with destruction of the joint and marked general symptoms. This group associated with sepsis is often fatal, even when treated surgically.

Gastro-intestinal System.—Pneumococcus infections of the mouth are medical curiosities.[95] A case of severe pneumococcus infection with GLOS-

SITIS was reported in 1903 and at that time was the second recorded instance of the condition.[96]

ACUTE PAROTITIS[97, 98] is rare and may develop at any time during the course or convalescence of pneumonia. The involvement of the parotid is generally unilateral, though occasionally both glands are affected. The infection may be hematogenous but probably more often is due to direct extension by way of Stenson's duct. The symptoms are fever, often chills, dry mouth and local pain, redness and swelling of the gland. These may subside spontaneously, or suppuration may follow with drainage of pus or rupture into the mouth. It may lead to facial paralysis, otitis, necrosis of the jaw and temporomaxillary joint, to jugular thrombosis and sepsis.

VOMITING with or without nausea may be a prodromal symptom, may attend the onset of the active disease or develop during the course of an attack. It is met with most often in children, in toxic cases, as a symptom of meningitis, as a consequence of medication, and in patients with gastro-intestinal or peritoneal inflammation. Pneumococcus gastritis, gastric and duodenal ulceration, enteritis and colitis rarely occur. Intestinal hemorrhages as a result of ulcerative lesions in the bowel have been described. Appendicitis may develop during the active disease or in convalescence.

ACUTE DILATATION OF THE STOMACH is an unusual and serious complication that generally escapes detection. The stomach may be tremendously distended and may even fill the entire abdomen. According to Fussel,[99] the dilatation is probably due to toxemia with resultant constriction of the duodenum and a secondary obstructive increase of the dilatation. The symptoms are vomiting, abdominal pain, distention, constipation, collapse, splashing sounds and visible gastric peristalsis. Untreated, the mortality is over 50 per cent., but when frequent lavage is practiced the prognosis is generally good.

METEORISM, often present in moderate degree, may become so marked as to be a serious complication, for when abdominal distention is great, serious interference with respiration may result. It occurs in very toxic cases, with sepsis, enteritis and peritonitis.

HICCOUGH is rarely sufficiently persistent and frequent to cloud the prognosis.

PERITONITIS is one of the very serious complications. Fortunately it is rare and does not develop in more than 0.5 per cent. of the cases. It may be primary or secondary, general or local. The primary localized form is most common in children and is diagnosed by the association of high fever with a tender abdominal mass and diarrhea. The secondary diffuse form is a metastatic manifestation of sepsis and develops during the same stage of the disease as pericarditis and empyema. The symptoms are those of peritonitis of other origin and whenever, with fever and leukocytosis, hiccough and vomiting are present with abdominal pain, rigidity, muscle spasm and tenderness, the diagnosis is clear. Abdominal pain and rigidity associated with pleurisy may lead to an incorrect diagnosis, but the latter symptoms usually appear early and disappear within a few days of the onset of pneumonia, whereas the symptoms resultant from a true peritonitis do not generally appear until the height of an attack. Moreover, true muscle spasm and persistent vomiting are helpful differential guides. It is especially important that in every patient with the symptoms of acute intra-abdominal inflammation a careful examination of the lungs be made, if the embarrassment of an unnecessary laparotomy in pneumonia is to be avoided.

JAUNDICE develops occasionally during the course of pneumonia and is said to occur in from 2 to 11.5 per cent. of the cases. Statistics probably fail to convey an accurate idea of its frequency, as the very mild grades are often undetected.

The incidence varies in different epidemics, and the degree of jaundice that develops shades from a subicteric tinting of the scleræ to outspoken yellow or rarely greenish staining of the skin and visible mucous membranes. It is usually first apparent at the height of the disease and is more common in the toxic cases. The stools generally contain bile, but instances of catarrhal obstruction of the bile ducts with acholic feces are recorded. The mortality of the cases with jaundice is higher than in uncomplicated pneumonia and is generally placed above 50 per cent. Probably the higher death rate is due not to the complication itself but to the conditions that caused it.

The actual causation of the jaundice is not established. Banti[100] regarded it as the result of a specific hemolytic action of the pneumococcus upon the erythrocytes and his experimental observations lend support to that idea. McPhedran[101] noted an increased corpuscular resistance of the red cells in the cases with most marked jaundice, bilirubin in the urine of jaundiced patients and a destruction of red corpuscles that he regarded as due to the pulmonary hepatization.

The view that it results from an infective cholangitis finds support in the occasional development of cholecystitis, but in McPhedran's cases autopsy showed no special changes in the liver. The idea that chronic passive congestion of the liver is the causal factor is negatived by the absence of signs of cardiac embarrassment and venous stasis.

INVOLVEMENT OF THE GLANDS OF INTERNAL SECRETION is very rare, but reports of thyroiditis, abscess of the thyroid gland and of purulent infection of the testicles appear in the literature.

PNEUMONIA IN ASSOCIATION WITH OTHER DISEASES

Infectious Diseases.—INFLUENZA.—Influenza may be complicated by the development of lobar or bronchopneumonia, and the pneumonic process may be but another manifestation of infection with the primary invader or the result of secondary infection with the pneumococcus, streptococcus or some other microörganism. Mixed infections are not uncommon. It is still a moot point as to how frequently the pulmonary consolidation is due to the *Diplococcus pneumoniæ*, but it is established that when the lesion in the lungs is truly lobar it is generally due to that agent. The influenza bacillus has never been shown to be the etiological agent in lobar pneumonia. The course of pneumonia complicating influenza is modified in that there is less often a chill at the onset, the fever is more irregular and often declines by lysis, the prostration and cyanosis are more marked, the pulse is slower, the sputum less often rusty and there is usually a leukopenia. The mortality is very great.

Malarial Fever.—In malarial fever pneumonia may develop as a complication and it is practically always due to the pneumococcus. When it does occur, the prognosis is grave, the mortality high and the course is often characterized by obscure physical signs, by prostration and by cerebral symptoms. Pulmonary congestion may be a source of confusion, and it is differentiated by its basal localization and intermittent fever. Pneumonia is never due to the malarial parasite.

Typhoid Fever.—Pneumonia is an uncommon occurrence in typhoid fever and when it develops is more often lobular than lobar in type. Generally due to infection with the pneumococcus, apparently authentic instances of pneumonic consolidation due to the *Bacillus typhosus* are recorded.

The pneumonia rarely occurs early in the course of typhoid fever, and when it does, its symptoms are characteristic and the existence of the latter may be first suspected because of the absence of leukocytosis, the protracted fever, the appearance of the roseola at the end of the first week; or the result of blood cultures may establish its presence. The onset of pneumonia is most frequent after the second week of the disease and it may not be detected. The pathognomonic features are often lacking and the presence of the complication may be indicated only by the accelerated respiration, cyanosis, tachycardia and leukocytosis. The latter may be relative to the preëxistent leukopenia and not absolute. Cough and expectoration may be entirely absent. The mortality in this group is unusually high. Finally, pneumonia may develop during convalescence and when it does there is seldom any diagnostic difficulty.

Occasionally the signs of pulmonary infarction are wrongly interpreted as indicative of pneumonia, and this is true especially when the signs of peripheral thrombosis are not evident or do not appear until after the lesion in the lung has become manifest.

Measles.—Measles is rarely complicated by the development of lobar pneumonia, but bronchopneumonia frequently occurs during convalescence. The pulmonary complications and sequelæ have been studied in our army cantonments and it has been demonstrated that post-measles bronchopneumonia is usually due to the *Streptococcus hæmolyticus*, and occurs most often in individuals who harbor that organism in their throats.

Scarlet Fever; Diphtheria.—Lobar pneumonia is very unusual as a complication of the other acute exanthemata and in scarlet fever is a very grave event, especially when there is a coexistent nephritis. In diphtheria pneumococcus pneumonia happens even more rarely.

Pulmonary Tuberculosis.—In the course of pulmonary tuberculosis pneumococcus pneumonia is a rarity, and when it develops, differential diagnosis is extremely difficult. Subacute and acute tuberculous consolidation present the same signs and often are attended by the same symptoms as pneumococcus pneumonia, though generally the history and the course of the disease are different. Exposure to infection, especially in childhood, evidences of tuberculous lesions in the lungs or elsewhere, a previous attack of idiopathic pleurisy—especially if attended by effusion—poor general health and frank hemoptysis are helpful differential points. Further, defervescence by lysis and low-grade leukocytosis with evidence of apical disease also speak for tuberculosis. The demonstration of tubercle bacilli in the sputum is conclusive evidence of the nature of the infection. Lobar pneumonia may lead to a flare-up of an inactive lesion or may be followed by a generalized dissemination of the tuberculosis, though probably in many cases the further course of the old disease is uninfluenced.

Non-infectious Diseases.—Diabetes.—When lobar pneumonia occurs in this disease it usually runs an atypical course and has a grave prognosis.[102] During the course of the infection glycosuria may be lessened or even disappear, but the danger of gangrene is increased and the patients usually die in coma.

Cardiac and Renal Disease.—In this group of cases bronchopneumonia is more frequent than the lobar variety. When the latter does occur, it may be confused with pulmonary congestion or infarction in cases with cardiac decompensation, and may be overlooked. The course of pneumonia in these diseases is very atypical, with insidious onset, slight pyrexia and abundant frothy sputum. The mortality is high.

Alcoholism.—In those addicted to the use of alcohol pneumonia occurs frequently and is a very fatal disease. It has an insidious onset, an afebrile or slightly febrile course, marked nervous symptoms and generally atypical manifestations. Delirium tremens is precipitated often early or at the height of the pneumonia.

Heat Stroke.—Heat stroke may be complicated by pneumonia and when it is the outlook is very grave, as over 50 per cent. have a lethal termination.

Insanity.—In the insane the symptoms are often very atypical and the disease may be readily overlooked.

CLINICAL VARIETIES—TYPES

The manifestations of lobar pneumonia are protean and, in addition to the classical entity described, there are a number of other clinical varieties.

Central Pneumonia.—When the consolidation begins in the depth of the lung, or at the hilum, and no part of the periphery is involved, the condition is termed latent or "central pneumonia." The former is the more suitable name, for often the condition is overlooked or, as the signs of consolidation may be lacking, the condition is only suspected from the history, the rusty sputum, accelerated respiration, fever and leukocytosis. Diagnosis in such cases is sometimes established by the *x*-ray. When the consolidation spreads to the surface of the lung the classical signs appear.

Massive Pneumonia.—Massive pneumonia is the term applied to consolidation of the lung with associated plugging of the bronchi. The physical signs are often those of pleural effusion, from which it may be differentiated by the appearance of the signs of consolidation following cough, the absence of Grocco's sign, the presence of resonance adjacent to the spine on the affected side, and often by the absence of displacement of the heart or other viscera. Occasionally, the signs are so equivocal that exploratory thoracentesis or a roentgenogram is necessary to exclude a pleural exudate.

Apical Pneumonia.—Apical pneumonia is considered by some an especial type of the disease, characterized by delirium, often indistinguishable from mania à potu, by stupor, and by hyperpyrexia. It is more common at the extremes of life, involves the right lung more often than the left, and pericarditis is said to occur more often as a complication than in other types of pneumonia. It is questionable, however, if there is any justification in setting apart pneumonia involving the apices as a clinical variety.

The *mortality of the three foregoing types* is essentially the same as that of ordinary lobar pneumonia.

Migratory Pneumonia.—Migratory pneumonia is an uncommon variety of lobar pneumonia in which different lobes or portions of lobes of the lungs are involved in succession. As resolution is established in one area, consolidation begins in another, the process spreading in contiguous portions of the lung. Several lobes may be involved and the disease run a protracted course. Oftentimes when the consolidation spreads to the previously healthy side a more marked exacerbation of symptoms occurs than when the progression is on the same side.

Short Term, or Abortive, Pneumonia.—This form is occasionally seen.[103] The onset of the disease may be typical, the signs of consolidation of a lobe complete, and crisis with subsidence of symptoms begin on the first, second or third day. The most striking instances of "one-day pneumonia" seen by the writer occurred in two young men, roommates, the second of whom contracted the disease apparently by direct contagion while nursing the first. In each the disease was of sudden onset, with chill, fever and pleural pain; each developed signs of complete consolidation of the right lower lobe, and in one the crisis occurred within 22 hours, in the other within 36 hours of the beginning of symptoms.

Senile, or Asthenic, Pneumonia.—Pneumonia in the aged or in individuals debilitated by chronic disease is characterized by the absence of prodromata, an insidious onset, severe prostration, absence of cough and expectoration, and often by the presence of coma, stupor or delirium, and by gastro-intestinal symptoms, especially nausea, vomiting and diarrhea.[104] The latter symptoms may be so striking as to dominate the clinical picture and lead to carelessness in examination of the chest. The only symptom in many cases is accelerated respiration, or dyspnea, and fever may be absent thoughout the course of the illness. The absence of other symptoms, and because physical signs of consolidation may be lacking for several days, explain the frequency with which the existence of pneumonia is overlooked in many of these patients. Occasionally typhoid fever is suspected but it can be readily excluded. The course is usually protracted. If there is fever defervescence is generally by lysis. Gangrene and abscess of the lung are frequent complications. The mortality is high.

Terminal, or Terminating, Pneumonia.—Terminal, more aptly termed terminating, pneumonia presents often the same characteristics as does the so-called asthenic type. Most usually met with in the aged, the alcoholic and in patients with chronic diseases, it is not uncommonly first recognized at autopsy. An afebrile course, without cough or dyspnea, and with slight constitutional symptoms, is not uncommon. Bronchopneumonia is more common as a terminal pulmonary complication than is the lobar variety.

Pneumonia in Infancy and Childhood.[105-111]—Though of less frequent occurrence than bronchopneumonia, lobar pneumonia is by no means uncommon in very early life. Holt states that after the age of three years all primary pneumonia is of the lobar variety and, according to Dunlap's statistics, it is met with as often in infancy as in later childhood. Many instances of antenatal pneumonia are recorded (MacDonald).

The disease is more common in boys than in girls. The mortality in infants is high (20-35 per cent.) and in children above the age of three years is low (2-10 per cent.). The duration is usually shorter than in adults, averaging seven days, and abortive pneumonia is not infrequently seen. The temperature is likely to be higher and more irregular than in adults, defervescence by lysis is more usual, and pseudo-crises are less common. Hyperpyrexia is not necessarily a grave prognostic sign in children. Chill at onset does not often occur, delirium and convulsions are frequently the initial symptoms, but vomiting and other gastrointestinal symptoms usher in the disease perhaps even more generally.

Very important for diagnosis is the altered pulse-respiration ratio from 4:1, to 3:1, or in infants even 2:1. The character of the respirations is considered by some to be pathognomonic—inspiration, pause, expiration, grunt—this modification occurring with tachypnea of 50 to 100 respirations per minute. The child is listless and fretful and infants often are disinclined to nurse. Erythemata are often seen; herpes is rare.

The physical signs may be indefinite or even absent during the early days of the disease and may not appear until the time of or even after the crisis (Freeman).

Tympany on percussion and suppression of breath sounds are early signs, and these may be first elicited high in the axilla. Often râles and dullness appear first, late in the course of the disease.

The explanation of the paucity of early signs, their appearance in the axilla and, in some instances, failure to detect their presence at all has been furnished by roentgenographic studies. These show that the pneumonic process always begins at the surface of the lung as a triangular wedge with the base at the periphery. Signs may be lacking at first, owing to the small size of the lesion, to the fact that it does not reach a large bronchus, or to its location high in the axilla or behind the scapula, shoulder-joint, or at the base of the lung.

The physical signs usually clear rapidly at the time of lysis or crisis and the persistence of them often is indicative of complications.

Pain referred to the abdomen is more frequent than in adults. Rigidity of the upper extremities and neck is often due to soreness of the chest.

Cough may be a valuable diagnostic symptom when the physical signs are obscure.

Meningismus is very frequently noted, but meningitis, though a more common complication than in adults, does not develop in a large percentage of the cases. Absence or diminution of the knee-jerk speaks against the existence of true meningitis. Otitis media and empyema are the most usual complications.

In children, lobar pneumonia may be indistinguishable from bronchopneumonia. The disease may be overlooked if it is not remembered that cough may be slight or absent, that the sputum is swallowed and that the physical signs of consolidation may be so obscure as to escape any but the most painstaking examination.

Postoperative Pneumonia.—Pneumonia develops very occasionally following operations, whether performed under general or local anesthesia. In most instances it is of the lobular variety but rarely a lobar pneumonia occurs postoperatively and the mode of its production is still moot. Exposure and chilling during the operative procedures, antecedent infection of the mouth and upper respiratory tract, bronchitis acute or chronic, may be predisposing factors. The presence of virulent pneumococci in the buccal, nasal or pharyngeal cavities, i.e., a carrier state, may be responsible in occasional instances; and when general anesthesia is induced with ether or chloroform the irritating action of the vapor may open the way for infection. In many cases the disease results from aërogenous infection through aspirated mucus or saliva, though it may rarely be of hematogenous, lymphogenous or embolic origin.

Pasteur has described a condition of extensive collapse of the lung resulting from paresis or paralysis of the diaphragm, and this condition may precede the onset of pneumonia or may be confused with it in the absence of consolidation. It involves the lower lobes most often, and when it occurs suddenly may be fatal.

Postoperative pneumonia is more common in the aged, the debilitated and after operations on the stomach, mouth, the respiratory tract and after gynecological operations.

The condition is rare, as shown by the statistics of Musser and Norris,[112] according to which it occurred in 0.35 per cent. of 139,101 collected cases.

Abscess of the lung is the most frequent complication.

Pneumonia in Pregnancy.—Pneumonia is a relatively infrequent complication of pregnancy, occurring in less than 1 per cent. of collected cases, but when it develops it materially increases maternal mortality and often leads to premature labor or abortion. Musser and Norris state that "if abortion does not occur in the first few days the prognosis is better" and "that the third day is the most common one on which abortion occurs."

Abortion or premature labor occurs in more than half the cases and when it does the maternal mortality is increased, due in part at least to the cardiac exertion incident to it. The frequency of abortion and the maternal death rate increase directly with the duration of the pregnancy, and even when gestation is seven months or more advanced the infant mortality is high. Death of the mother may be due to sepsis, toxemia, or to severe cardiac strain.

The cause of the spontaneous emptying of the uterus may be toxic or may be the result of an embolic pneumococcal endometritis. Experimental evidence for the latter origin is furnished by the experiments of Aufrecht on pregnant rabbits.

Pneumonia is less common in pregnancy than are pulmonary embolism and infarction and it may be readily confused with them (*see* Diagnosis).

Traumatic Pneumonia.—Pneumonia following injuries of the chest wall has been described,[113] but it is of very infrequent occurrence. It may develop in individuals in whom the lung itself has not been penetrated and may follow crushing wounds. The mechanism of its causation is not established and it is still a question as to whether or not a frank pneumonia due to the pneumococcus follows trauma, though a number of apparently authenticated instances are described in the literature.

Pneumonia Following Immersion in Water.—Pneumonia due to this cause occurs occasionally and is generally of the lobular variety. True lobar pneumonia may develop. Etiologically, chilling and shock are of some importance. It is probable that in this group of cases the presence of pneumococci in the buccal cavity and upper respiratory tract is the direct determinant of whether or not aspiration of water will lead to pulmonary consolidation.

Typhoid Pneumonia.—This ambiguous, undesirable term should be abolished from our nomenclature. It is rarely clear whether it refers to pulmonary consolidation, the result of infection with the *Bacillus typhosus,* or to true pneumococcus pneumonia with symptoms resembling those of typhoid fever. Both conditions occur, though pneumonia due to the typhoid bacillus is a very rare disease.

Secondary Pneumonia.—Secondary pneumonia has already been considered under the caption of Pneumonia in Association with Other Diseases and, as has been stated, its signs and symptoms often deviate markedly from those that are met with in uncomplicated frank pneumonia.

Whenever in the course of any disease there is noticeable disturbance of the normal respiration-pulse ratio, the existence of pneumonia should be suspected. Even careful physical examination may then fail to disclose the signs of consolidation and the diagnosis must be made from the symptoms, the fever and the character of the respiration. Unless an investigation of all parts of the lungs is made, including the axillæ, the middle lobe, the regions covered by the scapulæ and the supraclavicular and infraclavicular regions, errors will be frequent. Oftentimes there is great difficulty in deciding whether the lesion is a bronchopneumonia, atelectasis, hypostatic congestion, pulmonary infarction, edema or a central pneumonia.

Organizing Pneumonia.—In rare instances the exudate, instead of undergoing resolution and resorption, becomes organized, leading to fibrosis of the lung. This occurs most often in cases of delayed resolution and leads to permanent impairment of the function of the affected area.

TREATMENT

Prophylaxis.—The failure to eradicate or to lessen the incidence of pneumonia has been due in part at least to the failure to recognize its usual mode of dissemination. Though it is perhaps true that in some cases the disease may arise from an auto-inoculation with pathogenic strains harbored in the mouth, the studies from the Hospital of the Rockefeller Institute have apparently established the fact that most often it is the result of infection from without due to contact, direct or indirect.

This statement is true of infections with Types I and II, which are responsible for over 60 per cent. of all pneumococcus pneumonias studied. These strains are very rarely present in the mouths of normal persons who have not been in intimate contact with patients and they persist for only a limited time in the buccal secretions of convalescents from the disease. Pneumococci are found in dust, but pathogenic types are never found except in the environs of patients ill with pneumonia or in the quarters of healthy carriers. The chief sources for the spread of pneumonia are patients with pneumonia, convalescents who harbor the organisms in their buccal secretions ("convalescent carriers"), persons who have acquired the organisms by intimate contact with patients ("healthy carriers"), and dust from the immediate surroundings of patients or carriers. Recognition of these facts in regard to the dissemination of pneumonia due to Types I and II pneumococcus, and the realization that auto-inoculation with a pathogenic strain present in the mouth may rarely occur furnish a basis for the prophylactic measures to be taken.

General Measures.—To prevent the spread of pneumonia the same general measures are needed as are helpful in lessening the dissemination of other infectious diseases. The public must be educated, adequate legislation must be had, and a well-equipped board of health is necessary properly to enforce enacted laws. The compulsory reporting of each case of pneumonia will furnish new and important data concerning the epidemiology of the disease, and the employment of laboratory procedures will offer wider opportunities for the use of specific treatment.

Each case of pneumonia is a possible focus for the spread of infection, and the measures of isolation helpful in controlling the dissemination of other contagious diseases should be instituted. Inasmuch as the buccal and **respiratory secretions** are the chief sources of contagion, they should be carefully collected and burned or disinfected. A 5 per cent. solution of **carbolic acid** or of **lysol** is useful for this purpose. Before removal from the room, handkerchiefs, bed and body linen, clothing, utensils, etc., should be **sterilized** by boiling or by the use of disinfectants. Thermometers and all other appurtenances of the sick-room should be kept separate from those used for other patients.

Since it has been shown that the environs of the patients are contaminated, **daily cleansing of the room** should be carried out in such a way as to avoid scattering of dust, and after convalescence the room should be thoroughly cleansed and aired. Hot soda water is an admirable cleanser and **sunlight and fresh air** are more valuable than fumigation.

Attendants of the patient are best protected by good habits of **personal hygiene** and by scrupulous care of the mouth and nose through the use of ordinary so-called antiseptic mouth washes. Kolmer and Steinfield [114] recommend, as especially efficacious, the following solution:

Ethylhydrocuprein hydrochlorid or quinin bisulphate, 0.005 grams.
Liquor thymolis, 5.0 c.c.
Distilled water, sufficient to make 50.0 c.c.

The wearing of a **gauze mouth and nose guard** likewise lessens the danger of infection.

The control of carriers, convalescent and healthy, is more difficult, for it is not practicable to isolate all those who harbor the organism. All known carriers of pathogenic types of pneumococci should be instructed as to their potential harmfulness and cautioned to **avoid coughing and sneezing**, without shielding the mouth, and to avoid **expectorating**, except into proper containers, and in the use of **mouth washes** which may be helpful in ridding them of the cocci.

Finally, individual cleanliness, in its broadest sense; recognition of the value of fresh air and sunshine and of the dangers of poor ventilation and improper housing; avoidance of excess and of exposure, especially when fatigued or when "suffering with a common cold"; and observance of all the rules of good hygiene are invaluable preventive measures.

SPECIFIC MEASURES.—*Vaccination.*—Though a rational basis for prophylactic vaccination against the pneumococcus has been established, attempts to carry out this procedure successfully have generally failed. These unsuccessful efforts in the past were undoubtedly due to a failure to recognize or to consider the different immunologic groups of the pneumococcus.

The earliest important studies along this line were those of Lister,[115] who studied the effects of vaccination among the mine workers at Kimberley, South Africa. He injected a large group of men with a triple vaccine made of the three types of pneumococcus that had been found responsible for the cases of pneumonia among the workers and noted a markedly diminished incidence of subsequent infection among them, as contrasted with that occurring among the unvaccinated. Lister utilized cultures that were killed by the action of a germicide and administered three subcutaneous injections at seven-day intervals, each dose containing six thousand million of the several types of pneumococcus.

More recently Cecil and Austin,[116] at the Rockefeller Institute and at Camp Upton, have carried out elaborate studies on the preparation and dosage of the vaccine and have inoculated more than 12,000 soldiers. Types I, II, and III pneumococcus were incubated 12-14 hours in 0.5 per cent. glucose broth and then killed by heating to 53° C. for half an hour. The culture medium was removed by centrifugation and the cocci were suspended in salt solution. Viewed from the standpoint of protection alone, they found this vaccine equally efficacious in single or multiple injections, provided the total dosage in each case was the same. Fewer local and toxic reactions followed the use of repeated small inoculations. The optimum immunity response was obtained after three to five moderate doses at three to seven-day intervals, or when seven small daily injections were given. The total dosage was six to nine billion of Types I and II, and four and one-half to six billion of Type III.

During ten weeks of observation of vaccinated cases no case of pneumonia developed among the men who had received two or more injections of vaccine, whereas in a control series of about 20,000 men there were 26 cases of pneumonia due to pneumococcus Types I, II and III.

The local sterile infiltrations that occasionally followed the injections disappeared spontaneously and were interpreted as an expression of cutaneous hypersensitiveness.

The results of this experience are striking and warrant an extensive application of the method.

For convenience of description the treatment of "pneumonics" may be considered under the headings: I. General; II. Symptomatic; III. Specific.

General Management.—In treating patients with pneumonia several facts must be borne clearly in mind.

Pneumonia is a self-limited disease and, depending upon the virulence of the infection and the resisting power of the host, may present a picture of the greatest severity or may be merely a mild abortive syndrome. The mortality varies in different epidemics, seasons and localities, regardless of treatment, and the same clinical picture may arise following infection with organisms other than the pneumococcus.

Failure to recognize these fundamental theses has led to unwarranted enthusiasm regarding the efficacy of various modes of therapy and, through reaction, to therapeutic nihilism. These facts granted, it is at once apparent that no therapeutic procedure can be established as of value until it has been widely tested in large series of cases occurring in different epidemics, and unless very definitely beneficial results are seen in these as contrasted with those obtained in untreated controls.

Proper measures of **isolation** should be taken.

The patient, placed in bed, should be thoroughly **bathed** and **kept clean.** A **culture of the blood and of the sputum** should be made promptly to determine the type of organism responsible for the infection. **Daily or more frequent examinations** of the patient are necessary to ascertain the extent and progress of the pulmonary lesion, the degree of intoxication, the condition of the circulatory system, the development of complications, etc. The posterior thoracic regions should be investigated even in the very ill, otherwise a pleural exudate may be overlooked. During these examinations **unnecessary exposure** of and **unneeded exertion** by the patient should be avoided. Cough is provoked less often if he is turned on to the diseased side. The sickroom should be large, quiet, bright and well ventilated, the windows open, except during examinations or treatments. The bed should be a single one and of a type to facilitate attention on the part of nurse and physician. The coverings should be sufficient to protect the patient but not so heavy as to incommode him or to interfere with respiration. The bedwrap should be a light woolen shirt or pajama, slit the entire length to afford easy access for examination. The patient should not be permitted to sit up even to wash or feed himself and all attendants should be instructed to spare him effort. If he must be removed from his home to a hospital the greatest care must be observed to minimize physical activity, active or passive, during transportation.

The best position in bed is that which gives the greatest comfort.

Visitors should not be permitted during the active stage of the disease.

The **temperature, pulse and respiration** should be charted every two hours, day and night. Rigid care of the **mouth, nose and lips** is necessary. The **teeth** should be cleansed at least twice daily; the mouth rinsed with a **mild antiseptic solution** (Dobell's solution, liquor alkalinus antisepticus, etc.), and if the lips are very dry or fissured the application of **liquid vaselin** flavored with peppermint is often comfort-giving.

The **total urine** should be collected and examined daily and the character and quantity of the **sputum** noted. Gauze used to wipe the nose and lips should be burned. Bed linen, sputum containers, thermometers and all utensils of the sickroom should be cared for as in other infectious diseases.

Drugs should not be administered unless there are definite indications. A dose of **morphin, codein** or of **Dover's powder** to relieve pain and restlessness may be administered, provided there is no marked impairment of renal function. **Cardiac depressants** and **measures that lower blood-pressure** are to be avoided. **Laxatives** may be given at the onset of the disease, if necessary. The best diuretic is **water or milk. Alcohol** should be given only in those cases in which it promotes appetite and helps digestion and in those addicted to the use of it. Small amounts of **brandy or whiskey** may be given elderly patients as a food or as a hypnotic.

Expectorants, diaphoretics and stimulants are not indicated as routine procedures.

The evidence concerning the value of **oxygen** in the treatment of lobar pneumonia is contradictory.[117, 118] Certainly open-air treatment is more helpful generally and oxygen fills only an occasional need in cases with circulatory asthenia and restlessness. The gas when used must be free of chlorin and must be passed through a wash-bottle before inhalation.

DIET.—The **diet** in pneumonia may be arranged according to the desire of the patient and with regard for his ability to digest it. The disease is of such duration that a few days of restricted intake will do no harm. When there is anorexia or when gastric disturbances are present a liquid diet, with feedings at intervals of two hours, suffices. In some cases from the onset, in others after the active febrile stage is past, a soft diet may be allowed, and in all cases when defervescence is established liberal meals with intermediate feedings should be given.

It is well to prohibit foods that cause distention, and if milk does not agree it may be peptonized, diluted with lime water or Vichy, or it may be given in the form of buttermilk, kephir, koumiss, malted or as junket.

Children must often be fed by gavage. In the aged it is well to give small amounts of food at frequent intervals.

The fluid intake should be liberal and it is well to have the patient take at least a quart of water daily in addition to the liquids in the diet. If water causes nausea, ginger ale, lemonade, grape juice, coffee, tea, albumin, etc., may be given in its stead.

HYDROTHERAPY.—**Hydrotherapeutic measures** are invaluable in the treatment of pneumonia. They not only bring about a lowering of the temperature with concomitant diminution of discomfort, but through the use of them the nervous system is calmed, the circulation is aided, the blood-pressure is raised, respiration is stimulated and increased elimination promoted.

The **tub-bath** is of little value, except in treating children. For children immersion for 5 to 10 minutes in a tub of water heated to 95° or 100° F. (35° or 37.8° C.) may be helpful if there are marked nervous symptoms. During the bath there should be **constant rubbing** of the body surface.

Cold sponges are the most generally useful. Sponging with cool or tepid water or with dilute alcohol may be repeated at intervals of 3 to 4 hours, regardless of the elevation of temperature. The extremities and trunk should be sponged separately and during the process massaged briskly, rubbing towards the body. A properly given sponging requires 15-20 minutes, during which care should be taken not to expose the patient to **chilling**.

Internal hydrotherapy—the taking of an abundance of water—should be ordered in every case to promote elimination.

Aërotherapy.—It is often difficult to convince the patient and his family that fresh air is a valuable accessory in the treatment of pneumonia and that temperatures of 60° F. (15.6° C.) are not harmful to the patient. The day of the overheated room with sealed windows passes hard. It lingers here and there with the use of the pneumonia jacket, poultices and the application of pastes to the chest. Regardless of the outside temperature, the **windows should be open** and whenever conditions allow the **bed** may be wheeled on to a **protected porch**.[119, 120] Of course, the clothing and covers should be sufficient amply to protect the patient, and nurses or other attendants should wear extra wraps. Fresh air makes respiration easier, stimulates the circulation, quiets the nervous system, promotes appetite and, according to statistics, lowers the mortality of the disease.

Treatment of Symptoms.—Chill.—The patient should be **warmly clad**, wrapped well with **blankets** and surrounded by **hot water-bottles** or an **electric pad**. A **warm drink or whiskey** may be given.

Fever.—Fever is a manifestation of infection and an evidence of the resistance of the host. Except when hyperpyrexia is marked or when the fever itself is a cause of discomfort, there is no object in seeking to reduce it. The use of **antipyretic drugs** is to be condemned, and **hydrotherapy**—external and internal—is the method of choice to give relief from this symptom.

Thoracic Pain.—Thoracic pain often distresses the patient to such an extent as to prevent relaxation or sleep, and may cause exhaustion. It is often relieved by the application of **cold** (ice-cap—Leiter's coil) **or of heat** (hot water-bag, electric pad) to the chest wall. The use of **counterirritants**, of **cupping**, or of **leeches** is undesirable. **Fixation of the thorax** with a taut binder may be helpful, and though similar relief is afforded when adhesive straps are used, the latter are objectionable because they interfere with examinations and often irritate the skin. When these measures do not avail a **sedative** may be administered. **Opium** and its derivatives, **Dover's powder**, grains 5-10 (0.325-0.65 gram), and **codein**, grain ¼-½ (0.016-0.03 gram), are of great value in pneumonia for they not only relieve pain but promote relaxation and sleep.

Cough.—Cough is a symptom that requires medication only when it is harassing. To check repeated unproductive paroxysms **codein sulphate**, grain ¼-⅛ (0.016-0.008 gram); **heroin hydrochlorid**, grain 1/12 (0.005 gram) or **morphin**, grain ⅛ (0.008 gram) hypodermatically or by mouth, may be given. Of these drugs heroin is the least desirable and it is to be used with great caution. **Expectorants** are rarely helpful. In every case it is important to exclude a complicating **pleural effusion** as the provocative cause.

PLEURAL AND PULMONARY COMPLICATIONS.—The treatment of pleural and pulmonary complications (abscess, gangrene and delayed resolution) has been considered in the section on Complications.

CIRCULATORY SYSTEM.—The readiness with which signs of circulatory asthenia can be detected has led to the partly erroneous idea that the heart and vasomotor centers are materially damaged in pneumonia and to the failure to recognize the fact that the respiratory mechanism usually fails before the circulatory apparatus.

Anatomical studies have shown that the heart muscle is rarely diseased as a result of pneumococcus pneumonia and Porter has demonstrated that vasomotor paralysis does not occur.

The cardiac embarrassment is but another manifestation of infection and intoxication, increased in small measure only by mechanical disturbances in the lesser circulation.

To prevent circulatory failure all measures should be utilized that **lessen intoxication** and that **protect the patient.** Avoidance of physical effort, of excitement or annoyance; careful regard for every detail of comfort, the securing of the needed sleep and rest, the lessening of pain, cough, distention, etc., are valuable preventive aids.

Cardiac stimulants are invaluable both for the prevention and the relief of symptoms of circulatory embarrassment.[121] Of this group, **digitalis** and its derivatives are the most useful, for it has been shown that the pneumonic heart can be influenced by digitalis in the same way and with the same dosage as the normal heart.[122] Formerly it was considered good practice to withhold the administration of cardiac stimulants until evidences of cardiac failure developed (rapid weak pulse, arhythmia, marked fall of blood-pressure, increasing cyanosis, pulmonary edema, distended jugular veins, etc.). It is now recognized that considerable time is needed to bring about the effect of digitalis upon the heart and therefore it is wise to administer digitalis early, as a routine measure, in order that when the need for it arises, more prompt action may be had and the more dangerous intravenous administration of **strophanthin, digitalin, etc.**, may be avoided.

The **preparation of digitalis** to be employed is largely a matter of choice. The tincture may be used in doses of minims 10 to 15 (0.60 to 0.92 c.c.) three times daily, for a series of twelve or fifteen doses, when it is discontinued, to be repeated if an indication for it presents. One must be sure the preparation is an active one. When a satisfactory tincture is not to be had the powdered leaves, grain ¾ (0.05 gram), or infusion of digitalis, ½ ounce (15.5 grams), may be used. **Digalen,** 10-15 minims (0.60-0.92 c.c.), and **digitalin,** grain 1/60-1/30 (0.001-0.002 gram), are preferably administered hypodermatically.

Digipuratum is perhaps the preparation of greatest use because it is standardized and reliable. The administration of grains 7.7 (0.5 gram) digipuratum daily will digitalize the heart muscle within twenty-four hours, and when patients are seen early in the disease it is well to administer this dose on two successive days. The drug is then withheld until need for its readministration arises, when it may be given in the same amount until the stress is passed, though it is rarely wise to give over grains 38.5 (2.5 grams).

If there are any signs of circulatory weakness when the patient is first seen or if the disease has reached its height, grains 15.0 (1.0 gram) may be given during the first day. The prime indications for the use of digitalis are auricular fibrillation (pulse 150 to 200), other cardiac arhythmias and cardiac dilatation, and in these cases the most beneficial results are obtained.

When circulatory symptoms are urgent or when they develop abruptly, subcutaneous injections of **digitalin,** grain 1/60-1/30 (0.001-0.002 gram), or of **digalen,** 10-15 minims (0.60-0.92 c.c.), every four hours are helpful, or **strophanthin** (Boehringer), grain 1/120-1/60 (0.0005-0.001 gram), intravenously or intramuscularly may be life saving. Intramuscular injections are painful and may cause local induration, but these manifestations may be minimized by **deep massage** for at least ten minutes. Intravenous injections of strophanthin are not made without some danger to the patient,[123] and they are contraindicated in those who have received digitalis within the preceding thirty-six hours.

When signs of acute dilatation of the right side of the heart develop, prompt liberal **venesection** with the removal of 250-500 c.c. of blood often tides over the difficulty. When there is evidence of stasis in the lesser circulation with pulmonary edema, **atropin** is a valuable accessory to the foregoing measures. It may be given in doses of grain 1/150-1/200 (0.000433-0.000325 gram), at intervals of three or four hours, until the physiological action is noted.

Strychnin as a circulatory stimulant has not proved of great value in the writer's experience. There is a large and polemical literature on the worth of this drug in pneumonia that seems to indicate considerable confusion as to its real value.

Camphor, grains 1½ (0.0975 gram), in 1.0 c.c. sterile olive oil or **caffein sodium benzoate,** grain 1 (0.065 gram), may be given hypodermatically when a rapid transient stimulation is desired.

Nitroglycerin, adrenalin and **alcohol** are of doubtful utility.

The **aromatic spirit of ammonia** is useful when prompt stimulation is called for and especially in cases with distention, cardiac palpitation or paroxysmal dyspnea.

GASTRO-INTESTINAL SYSTEM.—*Anorexia* rarely requires treatment.

The *bowels* should be regulated throughout the disease. A **purgative** may be administered at the onset of the disease (sodium phosphate, Seidlitz powder, calomel, etc.) and during the course of the disease a **soapsuds enema** given daily or every other day will not only relieve constipation but will often lessen discomfort due to tympanites. When *distention is marked,* **restricted diet, enemata, hot stupes, turpentine stupes** or the use of a **soft rectal tube** passed high into the bowel and left in position for an hour or more will often suffice. If these measures fail, a **hypodermic injection** of **pituitrin** 1.0 c.c. is an excellent remedy.

For *acute dilatation* of the stomach **repeated lavage** is necessary. Incessant *vomiting* may be relieved by **limited diet, ice compresses** or a **mustard plaster** applied to the epigastrium, by **lavage** and by the use of **gastric sedatives.**

Colitis is relieved by **correction of the diet** and the use of **irrigations of the bowel** with solutions of salt, alum or boric acid.

Persistent hiccough may require the administration of **morphin.**

Peritonitis and other intra-abdominal complications of inflammatory nature demand **prompt surgical intervention.**

NERVOUS SYSTEM.—*Headache* is usually relieved by the local use of the **ice-cap** or of **cold compresses.** Less often drugs are indicated and then **acetyl salicylic acid,** grains 5 (0.324 gram), alone or with **codein sulphate,** grain ¼-½ (0.016-0.032 gram), or with **camphor monobromate,** grain 1 (0.065 gram), is usually effectual.

Insomnia may be relieved by the use of **hydrotherapy,** by the **relief of pain,** or it may require the use of **hypnotics. Codein or morphin** may be used; or if there is no cardiac weakness the usual dose of **sulphonal, veronal, trional or paraldehyd** may be given. **Chloral** is a depressant and must be used with great caution.

Delirium is quieted by **sponging** or by the use of the **sedatives,** already mentioned, though **morphin** is rarely of service. **Lumbar puncture** with withdrawal of small amounts of fluid is recommended when other measures fail.[124] In alcoholics it is lessened and may be prevented by the use of **whiskey, brandy, etc.,** and in these cases **depressant drugs** are contra-indicated. When an *exhaustion psychosis* develops, a **full diet** and **general upbuilding measures** are to be employed.

In every case with marked cerebral symptoms the presence of otic and meningeal complications and the development of sepsis must be excluded. *Meningitis* is a very fatal complication but the use of **specific antipneumococcus serum intraspinally** is indicated.

GENITO-URINARY COMPLICATIONS.—Genito-urinary complications are very infrequent. When nephritis develops it requires the same measures as do other forms of acute nephritis—**protection from chilling,** a **purin-free, protein-poor diet** with restriction of **salt,** regulated intake of **water** and stimulation of the excretory activities of the **skin and bowels.** In the very acute cases intravenous injections of solutions of **glucose** may be of value (100-500 c.c. of a 2 per cent. solution).

SKIN.—*The skin* requires the careful attention needed in all patients confined to bed. *Herpes* may be dried by the use of dusting powders such as **zinc oxid, stearate of zinc, etc.,** sedative washes such as **camphor water, compound tincture of benzoin, spirits of niter,** or ointments, as **oxid of zinc** with or without **cocain.**

THE CRISIS.—At the time of crisis, during it and after its occurrence, **protection and support** are needed. The patient must not exert himself; he should be kept recumbent, not allowed to strain at stool or to feed himself. If indicated, **stimulants** must be promptly administered in rapidly diffusible form. Hypodermic injections of **camphor in oil, caffein, sodium benzoate and atropin** are the ones of choice.

Warm coverings and the use of hot water-bottles, the electric pad or heat applied in other ways are often of use.

CONVALESCENCE.—Though the period of convalescence after a mild attack need not be long, several weeks of **rest** with abundance of **fresh air, a full diet** and slowly increasing periods of **exercise** should be taken. When the disease has been severe with marked intoxication or a prolonged course it is wise to refrain from working for a longer period, and an abundance of **rest, fresh air** and **good food** with **general massage** before active exercise is permitted are the best aids to complete recovery of normal strength. If cardiac or pulmonary complications have caused organic or functional disability, a proper régime should be ordered with **graduated exercise,** and **cardiac stimulants,** if there be circulatory asthenia; and **respiratory gymnastics** and **change of climate** if there is pulmonary impairment.

Tonics, hematonics, etc., are rarely needed, as anemia is uncommon after pneumonia.

TOXEMIA.—The manifestations of toxemia must be overcome chiefly by the use of general measures. They are often distinctly lessened by **hydrotherapy, aërotherapy, eliminants** and **stimulants.** Continuous or intermittent **enteroclysis of salt solution** is helpful: **hypodermoclysis** may be given, or if a more prompt effect is needed, **intravenous injections of salt solution** may be employed, after a preliminary venesection.

In some cases large doses of **alkali** (bicarbonate of soda 15 grains [1 gram] or more several times daily) seem effectual and these may be supplemented by the intravenous injection of a sterile 2 per cent. solution of **glucose** if acidosis is marked.

The usefulness of **alcohol** in cases with marked toxemia is moot, but there seems little doubt that its value is slight, if indeed it is not positively harmful. Collected statistics show a lower death rate when it is not administered.

When there are evidences of circulatory failure the procedures already outlined should be employed.

DELAYED RESOLUTION.—**Local and general measures** may aid in restoring the lung to function. **Counterirritants** are of doubtful value, **pulmonary gymnastics** (breathing against resistance, i.e., the use of water-bottles, etc.) are moderately helpful, and injections of **fibrolysin** are useless. The use of the **x-ray** has apparently a decidedly beneficial influence.[125, 126] **Thoracotomy**[127] has been recommended in some cases. The upbuilding of the patient, by the use of **overfeeding, rest** and **fresh air,** together with tonic preparations, such as **sodium cacodylate,** grain ¾ (0.048 gram), hypodermatically, **iron,** etc., hastens recovery.

Specific Treatment.—SERUM THERAPY.—Since Pasteur's observation that animals could be immunized against pathogenic organisms, and more particularly since von Behring demonstrated that it was possible passively to immunize animals by the injection of the serum of those treated with diphtheria toxin, numerous attempts have been made to produce an antipneumococcus serum with potent prophylactic and curative properties. The great obstacle to success was the fact that no soluble toxin could be isolated from the pneumococcus, and until it was shown experimentally that the injection of sublethal doses of living pneumococci protected against subsequent injections of lethal doses, the outlook for the production of an efficacious antipneumococcus serum was dark. Fränkel[128] demonstrated that an antiserum was responsible for the protection that resulted from such treatments and that though it was not antitoxic it could be used to immunize animals passively. The Klemperers,[129] in 1891, were the first to test the efficacy of such an antibacterial serum in the treatment of pneumonia, and their results stimulated further investigations, among the more important of which were those of Römer,[130] Pane,[131] Neufeld and Händel,[132] and the contributions from the Hospital of the Rockefeller Institute.

In 1904, Anders[133] concluded from a review of the literature that though the data were insufficient to justify optimism, they were sufficiently suggestive to warrant further investigations.

To Neufeld and Händel[132] belongs the credit for the preparation of a useful serum. They suggested the need of using large intravenous injections of virulent pneumococci to immunize animals, demonstrated the specific antigenic properties of the several types of the organism, and stressed the fact that a proper serum cannot be had for treatment until it is ascertained what particular strain is responsible for the infection in a given case. They also devised a method of standardizing the serum and recommended the intravenous administration of at least 75 c.c.

Dochez and Gillespie[134] isolated numerous strains of pneumococci, and on the basis of specific biologic relationships established the subdivision of pneumococcus into four definite types, I, II, III and IV, of which Types I and II are the two most often responsible for the disease, lobar pneumonia. The immunization of horses by intravenous injections of a given strain led to the production of an antiserum of fair potency against Types I and II and, with maximum power of protection, against other strains of the homologous type. As yet no satisfactory serum has been prepared for Types III and IV.

Inasmuch as a given antiserum is most active in protecting against infection with a strain of pneumococcus homologous with that by which it was produced, no constant therapeutic results are to be expected unless the type of pneumococcus responsible for the infection is determined; for only then can a proper antiserum be administered.

Practically, the procedure is as follows: After the clinical diagnosis has been made and the specific strain of the causal agent has been identified, the patient is given a subcutaneous injection of 0.5–1.0 c.c. of horse serum to test for the presence of hypersensitiveness. Even when this test is negative it is safer in all cases to give 1.0–5.0 c.c. of horse serum subcutaneously as a desensitizing dose before administering a large volume of the antiserum. The danger of anaphylaxis overcome, 50-100 c.c. of the warmed antipneumococcus serum diluted with an equal amount of sterile 0.85 per cent. salt solution are injected intravenously at the rate of 2-4 c.c. per minute. The injection is repeated once or twice daily until conditions indicate there is no need for further treatment. The only harmful effects that may result are those that so often follow the administration of foreign sera (serum sickness, q.v.).

A large number of cases of pneumonia have been treated by this method and the published statistics indicate that when the injections are given early in the disease due to infection with Type I pneumococcus, the results obtained are encouraging. In 65 cases treated at the Hospital of the Rockefeller Institute the mortality was reduced from 25 to 7.5 per cent.[135] In a series of 11 cases at the Johns Hopkins Hospital [136] the effect of similar treatment was less striking.

Following an injection the temperature may remain elevated, to fall by crisis at the customary time; or defervescence may occur gradually within a few days. Generally the course of the disease is shortened, the pulse is slower, the cyanosis less intense and the evidences of intoxication are less than in untreated cases. In many cases, within an hour or less after the administration of serum, there is a chill and a rise of temperature followed often by a sweat and an abrupt decline of the fever. A subsequent rise usually occurs and these phenomena may be repeated after each injection.

Delayed resolution and empyema are as frequent in serum-treated cases as in the untreated ones, but serum therapy apparently minimizes the danger of sepsis, and even when it exists the organisms disappear from the circulation after the serum is administered. Immune bodies are present in the blood immediately after the first injection and they can be demonstrated throughout the course of the infection if repeated treatments are given.

In brief, a serum has been prepared that is helpful in the treatment of pneumonia due to Type I pneumococcus, and the concentrated serum of Gay and Chickering [137] for disease due to Type II seems to be of some value. The way is paved for a serum therapy that may be useful in the treatment of an increasing number of cases of lobar pneumonia.

VACCINE THERAPY.—Vaccines have been used extensively in the treatment of lobar pneumonia. The object of this procedure is to stimulate the production of protective substances, and though there is evidence that this occurs in experimental animals, it is doubtful if a similar effect will result when a relatively small number of organisms are introduced into a host that is already infected. Interesting statistics have been published by Stoner,[138] Leary,[139] Craig,[140] Eyre [141] and others, but objective evidence of benefit following treatment with vaccines is not available, and until it is forthcoming it is difficult properly to estimate the value of the method. At the present time the usefulness of the procedure is not established.

Rosenow and Hektoen [142] noted beneficial results following the injection of **partially autolyzed pneumococci.** Treatment with vaccines of **sensitized pneumococci** has also been recommended.

CHEMOTHERAPY.—The number of drugs heralded from time to time as the remedial agent of choice in the treatment of lobar pneumonia speaks for the absence of specificity on the part of those utilized. **Guaiacol carbonate, camphor, creosote, quinin, the iodids, antimony, the salicylates, digitalis, iron and numerous other preparations** each has its champions. Each may have some value in the relief of symptoms; none is a specific curative agent.

Boehncke's [143] observations on the prophylactic value of **camphor** in experimental pneumococcus infections have not been confirmed clinically.

Morgenroth [144, 145] and his assistants noted that quinin and some of its synthetic derivatives protected mice against experimental infection with trypanosomes and discovered that a particular derivative of quinin —**ethylhydrocuprein**—possessed especially marked bactericidal action on the pneumococcus. Morgenroth showed this drug had not only great prophylactic value but marked curative properties as well in pneumococcus infections of mice, and obtained optimum results when it was administered in oil. Fränkel,[146] Moore,[147] Clough, Lapinsky [148] and others have confirmed these observations and ethylhydrocuprein or **optochin** has been used in the treatment of pneumococcus infections in men.

Moore and Chesney [149] recommended, in a man of average weight, an initial dose of grains 7 (0.46 gram) and grains 2⅓ (0.15 gram) every two and a half hours, until grains 23½ (1.5 grams) per twenty-four hours have been administered. From grain 0.37 to 0.4 (0.024 to 0.026 gram) of optochin per kilogram of body weight is needed to render the blood bactericidal, and the dosage should be calculated on the basis of the body weight. The drug is given until the symptoms of the disease subside, unless toxic manifestations due to the preparation itself develop. These latter are apparently dependent upon the concentration of optochin in the blood and are less likely to follow the use of repeated small doses. The action of optochin is cumulative.

The ocular manifestations resemble those noted in amblyopia due to quinin, and they may appear after a small total dose of the drug. Mydriasis, dimness or loss of vision, contra-indicate further administration. In marked cases there is pallor of the retina and narrowing of the retinal vessels. Blindness may develop and persist for a week or more, and though central vision is restored contraction of the visual fields may be permanent. But one case of permanent blindness has been reported.

The development of deafness is not a contra-indication to further treatment.

The available statistics "show a marked lowering of the mortality rate in a fairly large series of cases of lobar pneumonia. The results in the treatment of pneumococcus meningitis have been less favorable, but in ulcus corneæ serpens local applications of 1 to 2 per cent. aqueous solutions have been strikingly helpful." [149]

Extensive experimental studies to determine the effect of other derivatives of **cinchona** have been made by Solis-Cohen [150, 151] and his assistants. Though they demonstrated that quinin and its congeners possess some bactericidal action on the pneumococcus it was less than that of optochin. They were unable to establish an experimental basis for any beneficial action of these preparations.

PROGNOSIS

Pneumonia is always a serious disease and the prognosis must be a guarded one, for the apparently mild case may suddenly change for the worse and a manifestly severe case may as abruptly improve.[152]

Wells,[153] in an analysis of 233,730 collected cases, found a mortality rate of 18.1 per cent.; and in a later collection of 465,400 cases calculated a death rate of 20.4 per cent. This is the average in most large series of cases. The death rate varies between 20 and 60 per cent.

Accurate prognosis is determined only after consideration of many factors, general and individual.

Influencing Factors.—DOMINANCE OF TYPE OF PNEUMOCOCCI.—The severity and mortality of pneumonia vary greatly in different epidemics, regardless of location, physical conditions and of therapeutic procedure. These facts are frequently overlooked, and more than one season of mild disease with low mortality rate has led enthusiastic advocates of a mode of treatment to exaggerated claims for a *therapia magna.* It is possible that the variations in the mortality rate from year to year may be dependent upon the seasonal dominance of different types of pneumococci.

AGE.—The age of the patient is another determinant of the outcome of the disease. In general, the death rate is especially high in infancy and early childhood; there is a diminished mortality rate between six years and the age of puberty, and an increasing death rate above the age of puberty. The maxima occur at the extremes of life, and in the older patients the large number of fatal results are due to complications and to the existence of arteriosclerosis or to other chronic disease, manifest or latent.

SEX.—The death rate is higher in women than in men, as shown by Musser's figures of 26.9 per cent. for women and 19.3 per cent. for men.

PREVIOUS ATTACKS.—The mortality is lower in those who have had one or more previous attacks of pneumonia.

ALTITUDE.—The influence of altitude, long considered of importance, is recognized to be without influence on the course of the disease.

RACE.—The effect of race upon mortality is well shown by the statistics of the Johns Hopkins Hospital, by the studies of W. Kolle of pneumonia in the South African negroes, by a consideration of the death rate among the negro mine workers of the Rand, and among the laborers in the Panama Canal Zone. In the latter the mortality was highest among those most recently arrived in the country. The greater death rate is probably due to the unhygienic living conditions of the negro, the frequent presence of cardiovascular disease, of alcoholism and of syphilis as well as to a racial susceptibility to the disease. Jews and Italians have a smaller mortality, and according to the United States census reports, the mortality is higher in the foreign than in the native whites.

Complications.—The development of complications has a marked influence on the outcome of an attack of pneumonia and the earlier they develop in the course of the disease, the more serious the outlook.

Meningitis is almost uniformly fatal. Serous and serofibrinous pleurisy do not materially influence prognosis, but purulent pleurisy (empyema) has a higher death rate (35-40 per cent.). Acute endocarditis leads more often to a lethal result (60-70 per cent.) than does chronic endocarditis, and pericarditis, though less serious than the former, is a grave development (50-60 per cent. mortality). The occurrence of marked jaundice is a cause for concern.

Association with Other Diseases.—The influence of existing diseases on prognosis has been considered. It is most evident in individuals with valvular heart disease, chronic nephritis, diabetes mellitus, cirrhosis of the liver, arteriosclerosis, alcoholism and in malignant disease.

Clinical Manifestations.—The clinical manifestations give valuable prognostic data. An insidious onset; marked hyperpyrexia (except in the very young); a very slight febrile reaction; a pulse rate of more than 125 beats per minute in adults; an enfeebled pulmonic second sound, gallop rhythm, cardiac arhythmia or signs of dilatation of the heart; a marked or abrupt fall of blood-pressure, especially if associated with an increasing tachycardia; periodic respiration or a respiratory rate in adults of more than 50 per minute; extreme cyanosis; marked toxic manifestations; persistent abdominal distention; a poor leukocytic reaction and the presence of pneumococcal sepsis are of unfavorable significance. In many cases, though the general condition of the patient and the results of physical examination indicate a favorable prognosis, the results of blood cultures forecast conclusively an unfavorable outcome. The demonstration of more than a few colonies per cubic centimeter of blood, or the presence of Type I or Type II pneumococcus in the circulation is always of grave import as, too, is the demonstration of Friedländer's bacillus or the *Streptococcus mucosus.*

Relation of Type of Pneumococcus to Mortality.—The outcome of a given case of lobar pneumonia is influenced by the type of organism to which it is due, and though the severity of individual cases due to the different strains of pneumococcus varies, knowledge of the type of invading organism is of real prognostic value.

The statistics of the Hospital of The Rockefeller Institute show that the mortality of Type I infection is 25 per cent.; of Type II infection, about 32 per cent.; of Type IV infection, about 16 per cent.; and of infection due to Type III, 45 per cent. Types I and II, the etiological agents in over 60 per cent. of the cases included in this series, were responsible for about 62 per cent. of all deaths in the cases observed.

Location and Extent of Consolidation.—These factors have an influence on the outcome of the disease. Involvement of an entire lung is more fatal than disease of a single lobe; consolidation of an upper lobe has a higher death rate than consolidation of a lower lobe; pneumonia of the right side has an apparently greater mortality than pneumonia of the left side. These facts are admirably illustrated by the tabulated statistics of Sears and Larrabee:

One lobe	31 per cent.
Two lobes	38.2 per cent.
Three lobes	59.0 per cent.
Four lobes	62.5 per cent.
Five lobes	100.0 per cent.
Double pneumonia	42.5 per cent.

as well as by Preble's tables:

Right upper lobe	20.0 per cent.
Right middle lobe	14.7 per cent.
Right lower lobe	17.2 per cent.
Right lung	42.0 per cent.
Left upper	18.9 per cent.
Left lower	14.4 per cent.
Left lung	27.1 per cent.
Bilobar	36.2 per cent.
Bilateral	35.5 per cent.

Modes of Death.—Over 50 per cent. of the deaths occur between the fifth and the twelfth day of the disease. Sudden death may occur during the course of the disease or after convalescence has been established, due to sudden dilatation of the heart, to cardiac or pulmonary thrombosis. An abrupt termination may happen independently of the apparent severity of a given case and without relation to the extent of the pulmonary involvement.

Often the fatal result is foretold by a period of cardiac decompensation or by signs of increasing toxemia. More commonly, certain untoward symptoms herald the coming end. As early as the first day—most often at the height of the disease and uncommonly during convalescence—a patient who has been doing well may develop stupor, delirium, increasing polypnea, dyspnea and cyanosis, an increasingly rapid and weakened pulse or cardiac arhythmia. Signs of collapse appear with clammy skin, exhaustion, evidences of pulmonary edema, profound intoxication and a rise or fall of temperature just before death occurs. Death of this type is probably due to the development of pneumococcus sepsis or to an advancing infection of the lungs.[154]

The clinical syndrome known as "vasomotor collapse," characterized by evidences of marked vasodilatation, has been shown experimentally to be independent of exhaustion of the vasomotor center. The explanation for this complex is not established but it may be due to an undiscovered general infection.

Only when the making of repeated blood cultures in lobar pneumonia is established as a routine measure will there come an accurate and gen-

eral realization of the importance of sepsis as a cause of death in this disease.

Duration.—The duration of the disease varies considerably. The average duration of uncomplicated cases is from six to twelve days and it is rarely longer than three weeks. Abortive attacks are not uncommon, and true one-day pneumonia is occasionally seen. When complications occur, the course may be unusually protracted, especially in cases of delayed resolution, organizing pneumonia, pneumonia migrans and empyema.

In cases of sepsis, death may occur on the first day before the signs of pulmonary consolidation are manifest, but as a rule it does not occur before the fourth to fifth day.

Termination.—The febrile stage ends by crisis in over 50 per cent. of the cases, but though with the critical defervescence the subjective symptoms usually subside, signs of resolution do not appear immediately and an appreciable period elapses before the leukocytic curve and the excretion of urinary chlorids return to normal. In about a third of the cases the fever terminates by lysis or by retarded crisis.

Following crisis, there is often a short period of hypothermia that is of no significance unless it is prolonged and accompanied by tachycardia, when it may be indicative of exhaustion.

In typical crises the temperature reaches normal within 6 to 20 hours; but atypical crises occur, and 24 to 40 hours elapse before defervescence is established.

Pseudo-crisis is distinguished from true crisis by a recrudescence of fever after it has reached normal and remained so for several hours. It is usually followed by crisis within a day or two.

Termination by lysis is more common in some epidemics than in others and occurs more often in protracted cases, when complications have developed, in mixed infections, and in those with other acute or chronic diseases.

Relapse.—True relapses are rare in lobar pneumonia and it is in the abortive short-term cases that they are most likely to develop. The term should be used to describe those cases in which, after defervescence has been established and signs of resolution have appeared, evidence of a reconsolidation of the affected lung tissue develops with a recrudescence of fever. Several relapses, each usually of short duration, may occur. The term "recurrent pneumonia" is used to designate a second attack of the disease after an appreciable period of freedom from symptoms.

PATHOLOGY

Anatomically lobar pneumonia is characterized by inflammatory changes which take place in the lung, due to the action of pneumococci. These changes develop in a continuous sequence and it must not be inferred that, because traditionally these changes are divided into several **stages**, they are distinct or inherently different processes. For convenience of description the pathological processes are divided into a stage of engorgement, of red hepatization, of gray hepatization and of resolution, but it is rare to find solely the lesions characteristic of a given stage.

Stage of Engorgement.—This is the earliest manifestation of pneumonitis and is rarely seen at autopsy, except when a pneumonia is spreading or when the patient dies from some other cause than the pneumonia. The change is vasodilation with engorgement of the lung parenchyma and the exudation of serum with a few red corpuscles and leukocytes into the alveoli. The lung at this stage is deep red in color, its volume greater than normal; but though it is of increased firmness it is air-containing. The cut surface exudes a bloody serous material and microscopical examination shows engorged, distended capillaries, arteries and veins, swollen alveolar epithelium and coagulated serum with a few blood-cells, red and white. Fibrin is present but is inconspicuous. This stage of inflammation lasts but a few hours before red hepatization develops.

Stage of Red Hepatization.—In this, the second stage of hepatization, the involved lung is reddish-brown in color, voluminous, heavy, non-air-containing, and sinks when immersed in water. The surface has lost its normal sheen and is lusterless, often covered with a layer of fibrinous exudate. When sectioned it is found to be friable, firm, airless, and the cut surface is dry and very granular in appearance. When scraped with a knife very little moisture is expressed, but fibrinous plugs from alveoli and bronchi often rise above the surface. These vary greatly in diameter, depending upon the age of the patient and upon the presence or absence of antecedent emphysema.

On microscopical examination, the alveoli are seen to be distended with an inflammatory exudate very rich in fibrin, pneumococci, red corpuscles, leukocytes, desquamated alveolar epithelial cells, and often numerous wandering cells or lymphocytes. The fibrin is present as a network, in the meshes of which the cellular elements are trapped. The very distinctive feature of this stage, in addition to the amount of fibrin, is the freshness of the exudate and the preservation of the cells. The red cells are more numerous than in the later stages, are intact, clearly outlined, and show no evidence of hemolysis. The leukocytes are predominantly of the polymorphonuclear neutrophilic variety and often show engulfed pneumococci.

The alveolar walls, the peribronchial and perivascular tissues are edematous and infiltrated with leukocytes. The smaller bronchi may be plugged with fibrinous exudate. The blood-vessels may be patent, often they are compressed, and they may be occluded by thrombi. The lymphatics are distended with serum, fibrin and leukocytes.

Stage of Gray Hepatization.—In the stage of gray hepatization the color has changed to reddish-gray or gray. The lung is still enlarged, firm and non-air-containing. The surface is covered by a thick plastic exudate that can often be peeled off in layers from the adherent lung underlying it. The cut surface is mottled, the variations in color doubtless due to the laking of the red cells and the metamorphosis of the discharged hemoglobin. The tissue is more moist and a turbid fluid can be expressed from it. It is also less friable and is less granular in appearance.

On microscopical examination the alveoli are found closely packed with an exudate that consists mainly of polymorphonuclear leukocytes, pneumococci, both extracellular and intracellular, with relatively less fibrin and fewer red corpuscles. Especially distinctive of this stage, in contrast to that of red hepatization, is the cellular richness and the degeneration of the cellular elements of the exudate. Very few intact red corpuscles are found, but the shadows of the laked cells are seen. The leukocytes likewise show marked disintegration and some contain fat droplets and blood-pigment as well as pneumococci. In this, as in the preceding stage, fibrin threads may be seen passing through the alveolar walls through the so-called "pores of Cohn," and an occasional megalokaryocyte may be found within the alveolar capillaries. The fibrin is often granular by this time and the desquamated alveolar epithelial cells are numerous.

The capillaries of the alveolar walls are often extensively plugged with fibrin (Kline and Winternitz)—a factor that may be of importance in the process of resolution.

Stage of Resolution or Purulent Softening.—In this stage the enlarged lung is soft, friable, curiously translucent and jelly-like. This condition is rarely seen at autopsy, except in cases of pneumonia migrans and when death has resulted from an intercurrent infection. The striking finding on microscopical examination is the very advanced disintegration of the cells of the exudate, which are often quite fatty. Occasionally, marked phagocytosis is seen and there may be evidences of epithelial repair. The exudate is liquefied by the action of proteolytic enzymes furnished by the leukocytes, and the bulk of the inflammatory material is removed by absorption.

The stage of repair, of restoration of the alveolar epithelium after the removal of the exudate is even more rarely seen. It is remarkable how little involvement of the lung tissue itself occurs in pneumonia. The entire process seems to occur in the alveolar spaces and involves only the superficial epithelium of the air spaces, so that the complete restoration of the lung is readily brought about after the inflammation subsides.

Organization or carnification of the exudate may take place in exceptional cases. The exudate, instead of undergoing resolution and absorption, is invaded by blood-vessels and fibroblasts, with resulting fibrosis of the lung. The cells of the alveolar walls proliferate, new connective tissue grows into the exudate, capillaries form and a new fibrous tissue replaces the inflammatory tissue. The lung is now firm and elastic, reddish-brown in color and often covered with dense fibrous adhesions. When the exudate is thus replaced, the lung is essentially functionless and the condition is variously described as an organizing pneumonia, chronic interstitial pneumonia, pulmonary fibrosis or carnification of the lung.

Abscess formation is rare. Multiple small abscesses are the rule, though occasionally a single large subpleural one with very irregular outlines is formed which may perforate into the pleural cavity and cause a pyopneumothorax.

Gangrene is also a rare accident of resolution. It results from necrosis of the lung, usually due to secondary infection with putrefactive bacteria.

Distribution of the Changes in the Lungs.—The right lower lobe is the site of the pneumonic process more often than the left, and both lower lobes are less often affected than one alone. When two lobes are involved, the disease usually affects both lower lobes, though it may involve two lobes of one lung or the upper lobe of one and the lower of the other, or both upper lobes. An entire lung may be involved and rarely the changes are limited to an apex. The unaffected lung is often congested and the portions of the diseased lung adjacent to the consolidated area may be edematous. The larger bronchi show congestion of the mucous membrane and contain frothy mucoid or serous material, and fibrinous casts of a bronchial tree may be found. The bronchial lymph glands are swollen and are often quite soft.

Lesions in Other Organs.—The most common finding, apart from those already described, is dilatation of the right side of the heart. The right auricle and ventricle are usually filled with a tenacious clot, the like of which is rarely found in other diseases. There is cloudy swelling of the other viscera and in about half of the cases the spleen is appreciably enlarged.

HISTORICAL SUMMARY

Pneumonia was known to the ancients, and admirable descriptions of the disease are found in the writings of Hippocrates and Aretæus. The idea was general that all painless disorders of the chest were due to "peripneumonia" and it was not until the early eighteenth century that pneumonia and pleurisy were recognized as distinct maladies. This differentiation dates from the time when the study of pathological anatomy became a scientific practice, and more particularly from the time of Morgagni (1682-1771). Morgagni laid the real foundation of modern pathology and it was he who recognized the manifestations of pneumonia to be the result of solidification of the lungs. Baillie (1761-1823) designated the pulmonary change, "hepatization," and furnished the ground work for the epochal contributions of Auenbrugger (1722-1809) and of Laennec (1781-1826), whose observation led to the recognition of the disease by the use of methods of physical diagnosis and in turn made possible Rokitansky's differentiation between lobar and lobular pneumonia.

From this time until the late nineteenth century no great contribution was made except the elaboration of the physical signs and symptoms of the disease and the better recognition of the condition.

In 1874, von Jurgensen advanced the idea that pneumonia was an infectious disease due to a specific cause, basing his hypothesis largely upon the apparent incongruity between the local lesion and the severity of the systemic manifestations. Then came the era of bacteriology, the resolution of clinical complexes into etiological entities and the definite proof of the validity of Jurgensen's view.

Friedländer, in 1883, recovered an organism from pneumonic exudate with which he produced experimentally pleuropneumonia in mice and guinea pigs. He termed this organism the "pneumococcus" but subsequently it was identified as an encapsulated bacillus and a very unusual cause of lobar pneumonia.

In 1880 Sternberg, Surgeon-General of the United States Army, and Pasteur independently described the organism generally responsible for lobar pneumonia, but neither recognized its specific pathogenic properties.

To A. Fränkel (1884) is due the credit of establishing the pneumococcus as the causal agent of lobar pneumonia. He isolated it from the sputum of pneumonic patients, noted its regular presence in the pulmonary exudate and, with pure cultures, infected mice, guinea pigs and rabbits.

Fränkel's observations were confirmed shortly by Weichselbaum, who noted the occurrence of the pneumococcus in the blood and organs of a large series of cases in man; and subsequent routine examinations have completely established the validity of his observations.

With the further development of bacteriological investigation came the knowledge that lobar pneumonia may occasionally result from infection with Friedländer's bacillus or streptococci and rarely may be due to other organisms in the absence of the pneumococcus.

The succeeding twenty years brought refinements of the methods of diagnosis, the more general use of cultures of blood and sputum, immunological studies and futile efforts to discover a specific therapy. It was not until the beginning of this century that the path was blazed for the very modern procedures that are modifying our ideas of etiology and epidemiology of the disease and that are furnishing accurate prognostic data and a basis for a specific serum treatment.

Neufeld's subdivision of pneumococci into biological subgroups and the confirmation and extensive elaboration of his work by the workers at the Hospital of The Rockefeller Institute are of fundamental importance. Details of these observations are given in other sections of this article, but it should be stated here that, due to the discoveries of these investigators, the disease pneumonia is now better understood, knowledge of its mode of spread is more definite, prognosis is less problematical and the chances for the control and cure of it are greatly enhanced.

REFERENCES

General References

Aufrecht. Die Lungenentzündungen: in Nothnagel's Spec. Pathol. u. Therap. Bd. xiv, Teil I.
Fränkel. Spezielle Pathologie und Therapie der Lungenkrankheiten. Berlin, 1904.
Laennec. Traité de l'auscultation médiate. Paris, 1826.
Meara. Modern treatment (Hare and Landis). Philadelphia, 1910, Vol. I, pp. 707-737.
Müller, W. Deutsch. Arch. f. klin. Med., lxxiv, 111.
Norris. Osler's Modern medicine. Philadelphia and New York, 1913, 2d Ed., Vol. I, pp. 202-286.
Pye-Smith. System of medicine (Allbutt and Rolleston). London, 1909, Vol. V, pp. 191-254.
Staehelin. Handbuch der innere Medizin (Mohr u. Staehelin). Berlin, 1914, Vol. II, pp. 379-452.
Tendeloo. Studien über dis Ursachen der Lungenkrankheiten. Wiesbaden, 1904, Teil II.

Etiology

1. **Gorgas.** Jour. Am. Med. Assn., 1914, lxii, 1855.
2. **Stillman.** Jour. Exper. Med., 1916, xxiv, 651; 1917, xxvi, 513.
3. **Flick.** 3d Annual Report, Phipps Institute, 1907.
4. **Weichselbaum.** Wien. med. Jahrbücher, neue Folge, Jahrgang, 1886, 483.
5. **Eberth.** Deutsch. Arch. f. klin. Med., 1880, xxvii, 1.
6. **Fränkel.** Ztschr. f. klin. Med., 1886, x, 426.
7. **Heim.** Ztschr. f. Hyg., 1905, l, 120.
8. **Kraus, R.** Wien. klin. Wchnschr., 1897, x, 736.
9. **Dochez and Avery.** Jour. Exper. Med., 1917, xxvi, 477.
10. **Avery, Chickering, Cole and Dochez.** Monog. Rockefeller Inst. Med. Research, 1917, No. 7, 18.
11. **Dochez and Avery.** Jour. Exp. Med., 1915, xxii, 804.
12. **Stillman.** *Ibid.*, 1917, xxvi, 513.
13. **Wood.** Jour. Infect. Dis., 1912, xi, 623.
14. **Lamar and Meltzer.** Jour. Exper. Med., 1912, xv, 133.
15. **Cole.** Jour. Am. Med. Assn., 1912, lix, 693.
16. **Rosenow.** Jour. Infect. Dis., 1907, iv, 285.
17. **Neufeld and Haendel.** Ztschr. f. Immunitatsforsch., 1909, Teil I, 3, 168.
18. **Klopstock.** *Ibid.*, 1909-10, Orig. iv, 103.
19. **Strouse.** Jour. Exp. Med., 1911, xiv, 109.
20. **Wadsworth.** *Ibid.*, 1912, xvi, 54 and 78.
21. **Welch.** Bull. Johns Hopkins Hosp., 1890, i, 73.
22. **Clough.** *Ibid.*, 1913, xxiv, 295.

Symptomatology

23. **Norris.** Osler's Modern medicine. Philadelphia, 1907, 1st Ed., Vol. II, p. 563.
24. **Parkinson.** Brit. Med. Jour., 1917, i, 192.
25. **Dorning.** Tr. Am. Pediat. Soc., 1914, xxv, 316.
26. **Herrick.** Jour. Am. Med. Assn., 1903, xli, 535.
27. **Chatard.** Johns Hopkins Hosp. Rep., 1910, xv, 55.
28. **Pearce.** Jour. Lab. and Clin. Med., 1916-17, ii, 867.
29. **Lewis.** Lectures on the heart. New York, 1915.

30. **Peabody, F. W.** Jour. Exper. Med., 1910, xviii, 7.
31. **Hare.** Therap. Gaz., Detroit, 1910, xxxiv, 387.
32. **Lambert.** Jour. Am. Med. Assn., 1911, lvii, 1827.
33. **Tice.** Am. Jour. Med. Sc., 1916, clii, 91.
34. **Weigert, K. S.** Volkmann's Klinische Vorträge.
35. **Gibson, G. A.** Edinburgh Med. Jour., 1908, xxiii, 17.
36. **Newburgh, L. H.** Am. Jour. Med. Sc., 1915, cxlix, 204.
    Newburgh, L. H., and Minot, G. R. Arch. Int. Med., 1914, xiv, 48.
37. **Staehelin.** Handbuch der innere Medizin (Mohr u. Staehelin). Berlin, 1914, Vol. II, pp. 379-452.
38. **Parkinson.** Brit. Med. Jour., 1917, i, 192.
39. **Willson.** Jour. Am. Med. Assn., 1914, lxii, 982.
40. **Newburgh and Porter.** Jour. Exper. Med., 1915, xxii, 123.
41. **Norris.** Osler's Modern medicine. Philadelphia and New York, 1907, 1st Ed., Vol. II, p. 577.
42. **Howard.** Am. Jour. Med. Sc., 1903, cxxv, 256.
43. **Edgeworth.** Bristol. Med.-Chir. Jour., 1913, xxxi, 308.
44. **Lord.** Boston Med. and Surg. Jour., Feb. 2, 1914.
45. **Laehr.** Berl. klin. Wchnschr., 1893, i, 868-892.
46. **Ewing.** New York Med. Jour., 1893, xviii, 713.
47. **Emerson.** Clinical diagnosis. Philadelphia and London, 1906.
48. **Chatard.** Johns Hopkins Hosp. Rep., 1910, xv, 89.
49. **Cross.** Jour. Am. Med. Ass., 1915, lxv, 1778.
50. **Anders, J. M., and Meeker, G. H.** *Ibid.*, 1916, lxvii, 1591.
51. **Dochez, A. R.** Jour. Exper. Med., 1912, xvi, 692.
52. **Minot and Lee.** Jour. Am. Med. Assn., 1917, lxviii, 545.
53. **Peabody.** Jour. Exper. Med., 1913, xviii, 7.
54. ——— *Ibid.*, 1912, xvi, 701.
55. **Dochez.** *Ibid.*, 1912, xvi, 650.
56. **Pick.** Quoted by Lord. Verhandl. d. Naturforschergesellsch. Basel, Bd. xiii, 312.
57. **Palmer.** Jour. Exper. Med., 1917, xxvi, 495.
58. **Medigreceanu.** *Ibid.*, 1913, xviii, 259.
59. **Cook.** Bull. Johns Hopkins Hosp., 1902, xiii, 307.
60. **Chatard.** Johns Hopkins Hosp. Rep., 1910, xv, 55.
61. **Krehl and Matthes.** Deutsch. Arch. f. klin. Med., 1895, liv, 501.
62. **Ito.** *Ibid.*, 1901, lxxi, 35.
63. **Medigreceanu.** Jour. Exper. Med., 1911, xiv, 289.
64. **Peabody.** *Ibid.*, 1913, xvii, 71.
65. **Wolf and Lambert.** Arch. Int. Med., 1910, v, 406.
66. **Dochez, A. R., and Avery, O. T.** Jour. Exper. Med., 1917, xxvi, 477.

Diagnosis

67. **Mason.** Am. Jour. Dis. Child., 1916, xi, 188.

Complications

68. **Lord.** Diseases of the bronchi, lungs and pleura. Philadelphia and New York, 1915, 206.
69. **Musser and Norris.** Osler's Modern medicine. Philadelphia and New York, 1907, ii, 599.
70. **McCrae.** Johns Hopkins Hosp. Rep., 1910, xv, 167.
71. ——— *Ibid.*
72. **Gerhardt.** Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi, 695.
73. **McCrae.** Johns Hopkins Hosp. Rep., 1910, xv, 277.
74. **Flexner.** Tr. Assn. Amer. Phys., 1903, xviii, 359.
75. **Chatard.** Johns Hopkins Hosp. Rep., 1910, xv, 155.

76. Sears and Larrabee. St. Paul Med. Jour., 1902, iv, 451.
77. Weichselbaum. Wien. med. Wchnschr., 1888, xxxviii, 1176, 1209.
78. Forchheimer. Jour. Am. Med. Assn., 1909, liii, 1449.
79. Marshall. Johns Hopkins Hosp. Rep., 1910, xv, 139.
80. Edsall and Robertson. Proc. Path. Soc., 1903-1904, N. S., vii, 199.
81. Steiner. Johns Hopkins Hosp. Rep., 1910, xv, 89.
82. Frothingham. Arch. Int. Med., 1918, xxii, 74.
83. Osler. Maryland Med. Jour., 1897-98, xxxviii, 381.
84. Holt. Arch. Pediat., 1893, x, 1011.
85. Hanes. Johns Hopkins Hosp. Rep., 1910, xv, 247.
86. Weichselbaum. Wien. klin. Wchnschr., 1888, xxviii, 1177; 1209.
87. Guthrie. Proc. Roy. Soc. Med., London, 1913-14, vii; Sect. Stud. Di Child., 120.
88. Schultze. Deutsch. Arch. f. klin. Med., 1902, lxxiii, 351.
89. Witherington. Boston Med. and Surg. Jour., 1913, clxviii, 945; Am Jour. Med. Sc., 1914, clxvii, 203.
90. Libman and Celler. Am. Jour. Med. Sc., 1909, cxxxviii, 409.
91. Cave. Lancet, Jan. 12, 1901, i, 82.
92. Cole. Am. Med., 1902, iii, 905.
93. Slaughter. *Ibid.*, 1903, v, 605.
94. Herrick. Am. Jour. Med. Sc., 1902, cxxiv, 12.
95. Cary and Lyon. *Ibid.*, 1901, cxxii, 298.
96. Raw. Practitioner, 1903, lxx, 510.
97. Osler. Univ. Med. Mag., Philadelphia, 1893-94, vi, 245.
98. Norris. Philadelphia Med. Jour., 1901, vii, 790.
99. Fussel. Am. Jour. Med. Sc., 1911, cxlii, 974.
100. Banti. Centralbl. f. Bakteriol., 1896, xx, 849.
101. McPhedran. Bull. Johns Hopkins Hosp., 1911, xxii, 408.

Association with Other Diseases

102. Bussenius. Berl. klin. Wchnschr., 1896, xix, 420.

Clinical Varieties—Types

103. Bernhardt. Ztschr. f. klin. Med., 1880, Bd. i, 630.
104. Babcock. Jour. Am. Med. Assn., 1899, xxxiii, 438.
105. Chapin. *Ibid.*, 1915, lxv, 786.
106. Fleischner. Arch. Pediat., New York, 1915, xxxii, 165.
107. Holt. *Ibid.*, 1891, viii, 881.
108. Koplik. Boston Med. and Surg. Jour., 1905, clii, 741.
109. Morse. *Ibid.*, 1916, clxxiv, 131.
110. Northrup. Chicago Med. Rec., 1904, xxvi, 688.
111. Taylor. Brit. Jour. Child. Dis., 1907, iv, 373.
112. Musser and Norris. Osler's Modern medicine. Philadelphia and New York, 1st Ed., 1907.
113. Litten. Ztschr. f. klin. Med., 1882, v, 26.

Treatment

114. Kolmer and Steinfield. Jour. Am. Med. Assn., 1918, lxx, 14.
115. Lister. South African Institute for Medical Research. Publication, No. 8, 1916.
116. Cecil, R. L., and Austin, J. H. Jour. Exper. Med., 1918, xxviii, 19.
117. Osler. Principles and practice of medicine. New York, 1909, 7th Ed., 188.
118. Forchheimer. Prophylaxis and treatment of internal diseases. New York, 1910.

119. Norris. Am. Jour. Med. Sc., 1908, cxxxvi, 645.
120. Thompson. *Ibid.*, cxxxv, 13.
121. Ortner. Vorlesungen über specielle Therapie der innere Krankheiten. Berlin, 1900.
122. Cohn. Jour. Exper. Med., 1917, xxv, 65.
123. Babcock. Trans. Am. Clin. Assn., 1909, xxv.
124. Musser. Jour. Am. Med. Assn., 1917, lxviii, 1231.
125. Edsall and Pemberton. Am. Jour. Med. Sc., 1907, cxxxiii, 286.
126. ——— Tr. Assn. Am. Phys., 1906, xxi, 618.
127. Winslow. Surg. Gynec. and Obst., 1915, xx, 350.
128. Fränkel, A. Ztschr. f. klin. Med., 1885-86, x, 401.
129. Klemperer, F. and G. Berl. klin. Wchnschr., 1891, xxviii, 833.
130. Römer. Serum Therapie d. Pneumokokken Infektion d. Menschlichen Cornea. Wiesbaden, 1899.
131. Pane. Centralbl. f. Bakt. Orig., 1897, xxi, 664.
132. Neufeld. Ztschr. f. Hyg., 1902, xl, 54.
Neufeld and Händel. Ztschr. f. Immunitätsforsch., 1909, iii, 159; Berl. klin. Wchnschr., 1912, 680; Arb. a.d. k. Gsndhtsamte., 1908, xxviii, 572.
133. Anders. Jour. Am. Med. Assn., 1904, xliii, 1777.
134. Dochez and Gillespie. *Ibid.*, 1913, lxi, 727.
135. Avery, Chickering, Cole and Dochez. Monographs of the Rockefeller Inst. Med. Research, 1917, No. 7.
136. Bloomfield. Bull. Johns Hopkins Hosp., 1917, xxviii, 301.
137. Gay and Chickering. Jour. Exper. Med., 1915, xxi, 389.
138. Stoner. Am. Jour. Med. Sc., 1911, cxl, 186.
139. Leary. Boston Med. and Surg. Jour., 1909, clxi, 714.
140. Craig. Med. Rec., New York, 1912, lxxxii, 465.
141. Eyre. Lancet, 1908, i, 539.
142. Rosenow and Hektoen. Jour. Am. Med. Assn., 1913, lxi, 2203.
143. Boehncke. Berl. klin. Wchnschr., 1913, l, 818.
144. Morgenroth and Levy. Berl. klin. Wchnschr., 1911, ii, 1560, 1979.
145. Morgenroth and Halberstaedter. *Ibid.*, 1558.
146. Fränkel. Therap. d. Gegenw., 1915, lvi, 1.
147. Moore. Jour. Exper. Med., 1915, xxvi, 389, 551.
148. Lapinsky. Therap. Monatschr., 1915, xxix, 103.
149. Moore and Chesney. Arch. Int. Med., 1917, xix, 611.
150. Solis-Cohen, S., Kolmer, J. A., and Heist, G. D. Jour. Infect. Dis., 1917, xx, 272.
151. Solis-Cohen, S., Weiss, C., and Kolmer, J. A. *Ibid.*, 1918, xxii, 492.

Prognosis

152. Osler. Am. Jour. Med. Sc., 1907, cxiii, 1.
153. Wells. Quoted by Norris: in Osler's Modern medicine. 1906, Vol. II, p. 543.
154. Dochez. Jour. Exper. Med., 1912, xvi, 680.

CHAPTER VI

CEREBROSPINAL FEVER

By J. P. Leake, M.D.

Definition, p. 83—Etiology, p. 84—Epidemiology, p. 84—Prevalence, p. 84—Predisposing causes, p. 85—Manner of spread, p. 86—Bacteriology, p. 87—Pathogenesis, p. 89—Symptomatology, p. 90—Clinical history, p. 90—Period of incubation, p. 90—Mode of onset, p. 91—Subjective symptoms, p. 92—Physical findings, p. 92—Special and laboratory findings, p. 97—Spinal puncture, p. 97—Examination of blood, p. 102—Nasopharyngeal cultures, p. 103—Differential diagnosis, p. 103—Complications and sequelæ, p. 105—Clinical types, p. 106—Meningitis in early infancy, p. 106—Posterior basic meningitis, p. 107—Mild cases, p. 107—Ordinary acute cases, p. 108—Subacute and chronic cases, p. 109—Hyperacute and fulminating cases, p. 109—Treatment, p. 110—Prophylaxis, p. 110—General management, p. 112—Symptomatic treatment, p. 112—Serum treatment, p. 113—Surgical indications, p. 115—Treatment of complications and sequelæ, p. 116—Convalescence, p. 117—Prognosis, p. 117—Pathological anatomy, p. 118—Historical summary, p. 119.

Definition.—Cerebrospinal fever is a febrile, infectious disease caused by the meningococcus, a Gram-negative diplococcus present in the nasopharynx of many well people, but also capable of invading the leptomeninges in sporadic cases and in epidemics, and of producing a purulent meningeal inflammation with the more or less characteristic symptoms and signs of the disease. These are commonly fever of comparatively sudden onset, headache, stiffness of the neck, vomiting, prostration, leukocytosis, generalized tenderness, photophobia, mental clouding, irregular respiration, herpes and an eruption most frequently hemorrhagic (not disappearing on pressure). The first three of these symptoms, fever, headache and stiffness of the neck, are usual, the others less uniform; many cases of the disease may be seen before one is found with an eruption other than herpes.

The disease has been called by other names: cerebrospinal meningitis, epidemic cerebrospinal meningitis, epidemic meningitis, typhoid meningitis, malignant meningitis, meningococcus meningitis, meningococcus sepsis, meningococcus infection, spotted fever, petechial fever, black fever, jail fever, hospital fever, brain fever, spinal fever, tetanoid fever and epidemic cephalalgia. The term cerebrospinal fever is preferred as indicating a disease entity, apart from any necessary anatomic localization, and at the same time emphasizing the usual site of attack. Thus it is coming to be recognized that the disease may occur without a meningitis, yet with other symptoms and findings sufficient to establish its identity. This would invalidate the first six of the names in the above list. The term "epidemic meningitis," moreover, fails to take account of the ordinary sporadic cases. "Cerebrospinal meningitis" has been used by some in a broader sense, to include any inflammation of the cerebral and spinal meninges. "Meningococcus infection" and "meningococcus sepsis" are proposed by those who emphasize the systemic nature of the disease, yet these do not exclude such purely localized infections with the meningococcus as a conjunctivitis, an arthritis, or possibly a pharyngitis—infections which, though caused by the same microorganism, cannot be identified with the general disease. The other names are too indefinite and too little used at present to deserve more than the comment that their use should be entirely given up. The term "spotted fever" is especially obnoxious on account of its emphasis on an unusual symptom and its confusion with typhus, Rocky Mountain spotted fever, and with other eruptive diseases. Though still contending for a place with the infectious diseases in the International Classification of Causes of Death, the disease is listed as "Cerebrospinal Fever" in the 1918 American edition, and in the Bellevue Hospital Nomenclature, 1911 edition.

Etiology.—EPIDEMIOLOGY.—*Prevalence.*—In the absence of epidemics of cerebrospinal fever, the prevalence of the disease is to a considerable extent masked by confusion in diagnosis and in morbidity or mortality reports with other forms of meningitis. The non-epidemic incidence in American localities may be expected to be *less than 25 cases per 100,000* population per annum, with all cases accounted for, and outbreaks in large population centers do not usually go above five times this rate. Counting only a small group of inhabitants, such as a village or rural district, an outbreak may be so intense as to reach a 10 per cent. rate (10,000 per 100,000) per annum, but this is very rare.

Cases of cerebrospinal fever occur in all large communities throughout the year, but the characteristic seasonal prevalence is in *late winter and spring,* the epidemic and endemic peaks both occurring, as a rule, in January, February, March, April or May in the Northern Hemisphere, and in July, August, September, October or November in the Southern.

The disease is encountered both in the tropics and in the arctic regions, and records exist of outbreaks in all civilized countries, particularly in those of the north temperate zone. There have been *more epidemics* and a heavier sporadic incidence *in the United States than in any other nation.* This is especially striking if the European military epidemics be omitted from the calculation. It has long been noted that the assembling of troops in barracks gave rise to conditions which promoted the development of cerebrospinal fever, and many of the European outbreaks have been due to these conditions. The *English epidemics* of 1915, 1916 and 1917 were *primarily military,* for although considerably less than half of the 1915 cases occurred among soldiers, the civilian outbreak was by far more intense in those sections of the country where troops were quartered than elsewhere. The French army in the active zone, out of about 2,500,000 men each year, had 1,073 cases in 1915, 451 in 1916, and 409 in 1917. The complete figures for the American army are not yet available, but the heaviest incidence was in the training camps in this country, particularly in Camp Jackson, Camp Beauregard, and Camp Funston, the annual rate for the first being about 1,500 per 100,000 per annum; for the second, about 750, and for the third, about 500.

Though the sharpest outbreaks of cerebrospinal fever are not in large cities, the *heaviest incidence,* both epidemic and sporadic, is *in urban communities* rather than in rural. It is thus somewhat more characteristically a disease of cities than is poliomyelitis, which it resembles in many other ways. The meningitis outbreaks may be diffused over a rather wide area, but they are more commonly sharply limited and without obvious radial spread from epidemic centers. Such spread as occurs is usually by leaps, and irregular.

The *greater prevalence among males than among females,* usually shown in statistics, is without special significance, since men are assembled in large groups, such as armies, which are particularly prone to be attacked, and since practically all diseases which have a predilection for the very young are more frequent and more fatal in males. A greater number of male than of female babies are born, but the former die much more rapidly (Nichols, 1907).

Cerebrospinal fever is an *infection of youth.* About half the cases may be expected to be five years of age or under; the disease is more fatal in infants than in older children, and it is not improbable that many cases are undiagnosed on account of the equivocal signs in the very young. Cases may occur in the eighth decade of life, or at birth (Koplik, 1916; Sedgwick, 1915; Dandy and Blackfan, 1917), and in some epidemics the incidence is heaviest during later childhood or early adult life. It is interesting to note, however, that even in an English military area, where the gross morbidity indicated that the soldiers were the most susceptible, when the number of cases was compared with the number of individuals of each age group living in the area, it was found that the incidence was heaviest among the very young children.

Predisposing Causes.—The influence of *age* and of the *assembling of large bodies of men,* as in barracks, has been noted. In regard to the latter, two considerations may be of importance: intimate contact, as assisting in the transference of infection, and the imposition of unaccustomed tasks, as tending to decrease the resistance of the individual. Outbreaks do not occur among young men assembled at the beginning of a college year, but here physical toil is not a factor. Though epidemics have occurred among resting veterans, a large proportion of the military outbreaks have followed actual *fatigue* (Hirsch, 1886), especially in the case of recruits. The question of *overcrowding* has been brought to the attention of the English particularly, and Glover (1918, 2) has advised that beds in cantonments be at least two and a half feet apart. In the American navy, the factors of fatigue and exposure to cold have appeared to be of more importance than infection (Mink, 1918; Short, 1918) in determining the incidence of the disease in individuals. *Cold and damp weather* is thought to predispose to epidemics of meningitis, and attacks in some places have been said to have been preceded by "colds" or "influenza." It is certain that many outbreaks have not been correlated with particularly low temperatures or high humidities, and that no noteworthy rhinitis has preceded the greater number of cases.

An interesting observation has been made by Symmers (1918) that patients with *status lymphaticus* are prone to be attacked by a fatal form of cerebrospinal fever; 60 per cent. of the necropsies on cerebrospinal fever cases at Bellevue Hospital revealed status lymphaticus, while the incidence of the condition in necropsies on cases other than cerebrospinal fever was 8 per cent. The cases were fairly evenly divided among the different age groups. A similar predisposition was noted in Westenhoeffer's Silesian series of 29 necropsies.

Manner of Spread.—Cases of cerebrospinal fever usually occur, both sporadically and in epidemics, *without* demonstrable *direct contact* with other cases; spot maps show a scattered distribution throughout the localities affected. Doctors, nurses, or other patients do not ordinarily contract the disease from cases in hospitals. It is rare for more than one case to occur in a family, and instances of such occurrence are as likely to indicate simultaneous infection as infection of one case from another. In intense outbreaks familial and house distribution occurs; thus in Alexandria, Louisiana, eight cases and four deaths occurred in a family of nine, the father alone escaping. This was the neighboring town to Camp Beauregard, where a very fatal epidemic was in progress.

The explanation of this seemingly peculiar, but in fact not unusual distribution of an infectious disease, presumably spread by contact, lies in the evidence that *carriers* of the meningococcus are much more numerous than actual cases of the disease, and that the proportion of people who are ordinarily susceptible to the disease is very small.

Largely on the basis of German studies, it had been assumed that in the absence of epidemics, carriers were almost nil. English and American experience, and more recent German work, have indicated that even with material drawn from places where little or no cerebrospinal fever was occurring, the percentage of carriers might be 0.7 per cent. (Short, 1918), 1 per cent. (Bassett Smith, 1917), 2 per cent. (Mayer, Waldmann, Furst, and Gruber, 1910), 2 per cent. (Flack, 1917), 7 per cent. (Kutscher, 1906), 8 per cent. (Lewis, 1917), 10 per cent. (Griffith, 1916), 13 per cent. (Ponder, 1917), 14 per cent. (Scott, 1916), or even 25 per cent. (estimate of Fildes, 1918). Results are practically uniform that among "non-contacts" in epidemic areas, and particularly among "contacts"—i.e., persons who have recently been in close contact with actual cases of the disease—the proportion of carriers is higher than in persons from non-epidemic areas; it is also shown that the carrier rate generally rises at the season of the year when meningitis is most likely to be prevalent, and that conditions of overcrowding increase the carrier rate.

The actual manner of spread is therefore assumed to be usually by droplet infection from carrier to carrier, and finally to a susceptible individual who develops the disease.

BACTERIOLOGY.—*Morphology.*—The meningococcus, called at first *Diplococcus intracellularis meningitidis,* is an organism easily stained by the ordinary basic aniline dyes, but losing the stain when decolorized by Gram's method, and taking the counterstain instead. It disintegrates or autolyses very easily and except in smears from fresh young cultures may be seen in a variety of sizes and intensities of staining reaction; its Gram-negative nature is constant, when the staining and decolorization are properly performed, and serves to distinguish it from all other intact organisms (except Pfeiffer's influenza bacillus) which are commonly found as causes of meningitis. Other cocci, properly Gram-positive in young cultures, may show Gram-negative forms when older or when injured in any way. A satisfactory method of applying Gram's stain is to stain the smear with active carbol gentian- or methyl-violet for three minutes without heat, pour off the stain, apply the iodin-potassium iodid solution for one minute, pour off, or blot, decolorize by allowing successive drops of absolute alcohol to flow over the slide till the color comes out—this should not require more than two minutes with a thin smear—wash in water, and counterstain for only fifteen seconds with saffranin or with a one-in-ten dilution of carbol-fuchsin. It is well occasionally to control this stain by smears, on the same slide, of a known Gram-positive organism such as the diphtheria bacillus from an 18 to 24-hour culture at one end of the slide, and a known Gram-negative organism such as the typhoid or colon bacillus at the other.

Meningococci in fresh cultures are medium-sized oblong or kidney-shaped cocci, arranged in pairs with the broad side of each coccus facing the other coccus of the pair. Tetrads are frequently seen, but chains are unusual. In smears from the spinal exudate and from other sites of pathological invasion, the cocci are commonly, but by no means uniformly, found within polynuclear leukocytes. The predominance of free cocci is taken as a bad sign, since as cases progress toward improvement, the cocci become entirely intercellular.

Cultures.—In cultures the meningococcus, like the gonococcus which it resembles, prefers the enrichment of the medium with some animal fluid, and when first isolated will hardly grow without such enrichment. The media proposed, some containing serum or blood, and some without, have been very numerous. Growth on ascitic agar is usually prompt, the larger colonies reaching two millimeters or more in diameter in twenty-four hours, and presenting a rounded, moist appearance with smooth, well-defined edges; the color is a translucent gray at first, becoming whitish or slightly yellowish or brownish as the growth becomes more profuse, but showing no pronounced color with age; this cultural appearance is not always present (Conti. 1918). Moistness and freshness of the medium, with maintenance of a constant temperature, are requisites of success in growing meningococci. The organisms will not usually survive drying out, or any considerable fluctuations in temperature. Absence of growth at 23° C. has been held as one of the criteria for identifying the meningococcus. Ordinarily the meningococcus must be rather frequently transplanted to survive prolonged cultivation.

Typically the coccus ferments glucose and maltose but not saccharose, and this, together with its cultural characteristics as given above, serves to differentiate it from other Gram-negative cocci as a rule. The variation in intensity of these fermentations, together with variations in the media used, adds an element of uncertainty to such differentiation; provided the sugars are pure, the variation is in the direction of diminished fermentative power, rather than of increased.

Serology.—Serologically meningococci do not behave entirely as a unit, but show differences among themselves and resemblances to such allied organisms as the gonococcus. By agglutination Elser and Huntoon (1909) found marked differences in degrees of reaction, some strains being relatively inagglutinable. Arkwright (1909), from twenty-five epidemic and twenty sporadic strains, made more than three groups and subgroups. Dopter's parameningococcus (1909, 3) was the first generally recognized variant, and Dopter and Parron (1914) have since noted two other variants, calling the four groups meningococcus, parameningococcus alpha, parameningococcus beta, and parameningococcus gamma. The term "parameningococcus" is an unfortunate one, since any of the varieties given that name might as justly be called meningococcus as the original strain. Ellis (1915), of the Canadian forces in France, found two broad agglutinative groups, and a similar grouping is found by the workers of the English Local Government Board (Eastwood; Griffith; Scott, 1916 and 1917; Ponder, 1917), though as many as five or six subgroups might be recognized within a single broad group. In the hands of almost all workers, by far the greater part of the strains examined correspond more or less closely to one of two types. By the use of rapidly prepared monovalent rabbit serum for agglutination, and also by the absorption of agglutinins, Gordon and his co-workers in and from the Central Cerebrospinal Fever Laboratory of the Royal Army Medical College differentiated types I, II, III and IV as responsible for practically all of the meningitis among the English forces during 1915 and 1916. Using rapid agglutination at room temperature instead of the standard method of agglutination at 55° C. overnight, Nicolle, Debains and Jouan (1918) divided their strains into groups A, B, C and D, which they said corresponded, but not exactly, with Dopter's meningococcus, and paras alpha, beta and gamma respectively; they also found Gordon's types I and III falling in their A group, and II and IV in the B group. Correlations of these various European groupings among themselves and with the common American division (Amoss, 1917) into normal or regular, irregular and para strains have not been uniform and satisfactory, so that it is not possible to say that a given group in one system corresponds fully and completely with any group in another system. There are many cross relations and overlappings between groups; complement-fixation has in general given broader, less sharply specific reactions than has agglutination. A sharper degree of subdivision is possible by absorption of agglutinins than in any other way, but the practical significance of such subdivision may be questioned.

It has been shown that meningococci may be classified on the basis of their reaction to phagocytosis with specific sera.

The tropin group R corresponds roughly with Gordon's agglutinative types I and III, tropin group S with agglutinative Type II, and there are at least three other tropin groups, T, U and Z. There is some indication that the prevalent types are changing so that the sera for intraspinal therapy should be maintained representative of the various types encountered. This is done for American sera.

These considerations are of importance as regards the definition of the meningococcus when a Gram-negative diplococcus similar to the meningococcus is found in the nasopharynx, and as regards the polyvalency of serum to be used in the treatment of the disease (McCoy, 1918). American sera are required to have a broadness of action sufficient to cover all strains ordinarily encountered.

Experimental Research.—Some points in the proof that the meningococcus is the cause of cerebrospinal fever are lacking, but the evidence is so overwhelming as to be conclusive. The attempt by Hort to incriminate a filterable virus, although recent, has now only the historical interest which attaches to the former confusion of the pneumococcus with the meningococcus, and to the assignment by Jaeger and others of an etiological rôle to other, Gram-positive, cocci which we now look upon as contaminations. Though the meningococci are sometimes not to be found, the uniformity of the presence of cocci answering the description of meningococci in the spinal fluid of epidemic cases is too great to explain on any other grounds than that they actually cause the disease. Meningococci are irregularly pathogenic when injected intraperitoneally into certain animals, particularly young guinea pigs and white mice. Subdural injections have caused meningitis in rabbits, dogs, a goat, and monkeys, but such direct inoculation does not prove the elective localization which the meningococcus must show in human infection. Intraspinal inoculation of monkeys enabled Flexner to follow the action of antimeningococcic serum and gave a great stimulus to the use of the latter in human cases. Austrian (1918) succeeded in producing a typical fatal meningitis in three out of twenty rabbits inoculated intravenously with meningococci by giving a simultaneous intraspinal injection of normal rabbit serum. Weed, Wegeforth, Ayer and Felton (1919) have similarly caused the meningeal localization of *Bacillus mucosus capsulatus* injected into rabbits intravenously, merely by withdrawing spinal fluid through a lumbar puncture.

Pathogenesis.—There is no reason to doubt that the meningococcus reaches the body, and leaves the body, by way of the nasopharynx, where it is commonly found. That the meninges are invaded by direct extension through the ethmoid or sphenoid, as urged by Weigert and by Westenhöffer, is open to serious question. The regions of favorite localization at the base of the brain are not actually in relation with the nasopharyngeal sinuses, though thought at first to be so, and there is no communication between the lymphatics of these sinuses and the cerebrospinal system. The subarachnoid space with the ventricles and the perivascular and perineural spaces of the brain and cord form a closed sac, and lymph spaces are not found; cerebrospinal fluid takes the place of lymph within that part of the central nervous system which is enclosed by the dura mater. The experiments just related of Austrian, and of Weed, Wegeforth, Ayer and Felton suggest that the meninges are invaded by way of the blood, and this coincides with the occasional positive blood cultures early in the disease. It must be stated that the meningococci apparently do not as a rule multiply in the blood stream so as to constitute a true septicemia, but that they quickly seek their natural pathogenic habitat, the meninges, though other sites of lessened specific resistance are occasionally found. That the meningococcus has a relatively low pathogenetic intensity is shown by the fact that it is the only known pathogenic bacterium which can infect the meninges without producing practically 100 per cent. fatality.

It has been frequently held that the harmful effects of the meningococcus are due to "endotoxins," or poisonous bodies bound up with the bacteria themselves. Certainly autolysates, and various products formed by the disintegration of the microörganisms, may be very toxic. Whether the bodily defenses which overcome the disease are chiefly directed against such toxic products or against the living cocci is not known. Of the antibacterial forces, those known as bacteriotropins or opsonins, which promote the phagocytosis observed to be coincident with recovery, are of prime importance. There is no doubt that the factors of individual resistance or susceptibility weigh more heavily in determining whether or not an attack will take place than does the matter of chance infection.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—Our former ideas of a more or less definite period of incubation for each infectious disease have undergone some modification of late. In general, the more highly contagious the disease, the more definite the period of incubation, and cerebrospinal fever being of a low degree of infectivity, its period of incubation is variable and uncertain. The experience with military tetanus, for example, has demonstrated that the infecting organism may long lie dormant in a healed wound, to be stirred into activity by a subsequent operation or even by therapeutic exercises. So it is believed in some quarters that every case of cerebrospinal fever is first a carrier of the meningococcus in his nasopharynx, and that by a breaking down, perhaps temporary, of the barrier of defense, the coccus is enabled to invade the body and cause the disease. Flack (1917) reports 5 cases in the London district developing among carriers in from one to forty days after their isolation. Short (1918) reports 6 cases out of 1,228 carriers at Great Lakes Station. On the other hand, among 485 carriers in the British Navy at Portsmouth kept under observation by Fildes (1918) during an outbreak, not one developed meningitis. A similar absence of meningitis among carriers was found by Robey (1918), Redden (1918) and Landry (1919). On the rare occasion of more than one case occurring in the same family or among messmates, the cases may be separated by hours or months. The possibility of both cases being infected from a common source is to be borne in mind. More definite are the cases which develop in a previously non-infected district after a visit to or from an infected focus. Such evidence places the usual incubation period at from *one to five days.* The former corresponds to the case reported by Sophian (1913), apparently contracted at the necropsy on a malignant case; it is reasonable to suppose that a disease which can run such a rapidly disastrous course as the fulminating type of cerebrospinal fever may at times have a very short incubation period.

Mode of Onset.—The onset as a rule is *sudden;* the patient has enough fever and prostration to be kept in bed within twenty-four hours of the first clear symptoms. Premonitory indispositions occur, but one cannot say whether these are a part of the disease itself, or a lowering of resistance, due to another cause, and opening the way for a meningococcal infection. Ambulatory cases with a true meningeal headache are unusual. Koplik has described cases with intermittent onset and course. Intervals of entire remission of symptoms early in the course of the disease are not common in the experience of most observers, although the French writers and Foster and Gaskell have emphasized a lack of increase of symptoms or a clinical improvement in many of their cases on the second day, even without treatment. A normal temperature may be maintained for several days, and delay the diagnostic puncture. The temperature charts during the later course of the disease are often irregular, but the patients do not regain entire well-being in the afebrile periods.

An early catarrhal stage of the disease has been described in some epidemics, notably at Aldershot in England. Surveys of the nasal and pharyngeal condition at the onset, as well as in carriers, have not tended to substantiate the idea that an initial rhinitis or pharyngitis is notably more frequent or pronounced than in other fevers, nor that the meningococcus necessarily, or even commonly, sets up an inflammation in the throat. The conditions of overcrowding, stress and bad weather which frequently accompany epidemics of meningitis are apt to breed coryzas and similar infections.

A *chill* with rigor, or a convulsion in an infant, frequently ushers in the disease. The chill may be replaced by chilly feelings and malaise, or this period of invasion may be so masked or so soon succeeded by definite meningeal symptoms or unconsciousness as to escape notice. The convulsions are not usually prolonged beyond the first few days, and are very rare in adults.

Vomiting occurs in more than half of the cases at, or soon after, the onset. Though this symptom together with a not uncommon abdominal pain in children, often directs attention to the gastro-intestinal tract, the vomiting usually is not preceded by nausea and frequently bears no relation to meals. Vomiting is a symptom of the initial stages, and is not usual thereafter, in contrast to other cerebral diseases. In a disease with the severity of cerebrospinal fever it is to be expected that the appetite will be lost or very largely impaired; nutrition is therefore an important part of the treatment, particularly when the course is prolonged. Evidence of malnutrition may be seen as early as the fourth or fifth day, especially in hydrocephalic cases, which characteristically have abdominal retraction. Sleeplessness promotes the catabolism of the patients' tissues with resultant loss in weight. As a rule, the vomiting is not sufficiently prolonged to be a factor of much importance in this respect.

Subjective Symptoms.—Usually the first definitely meningeal symptom in an adult is *headache.* This may be referred to any or all parts of the cranium, frontal headache frequently giving way to occipital as the disease progresses. Not at first differentiated from an ordinary headache accompanying any general infection or toxemia, the headache of cerebrospinal fever typically becomes in intensity one of the most prominent symptoms unless supplanted by delirium or mental dullness or unless relieved by treatment. It is not stopped by ordinary methods, such as cool applications and mild analgesics; if the patient knows by experience the improvement following lumbar puncture he may beg for the latter, although it is to be performed without anesthesia. The fact that this characteristic symptom is definitely absent in some cases leads us to expect it to be mild in others, and to resort to lumbar puncture even if the headache is not present in its typical severity, provided other sufficiently significant indications are found.

The mentality at onset and in the early stages may be normal, with allowance for the prostration, pain and natural apprehension. Commonly the patient is either hypersensitive and irritable, or dull and unresponsive, though in the epidemic cases there may be delirium, stupor or collapse when first seen. During the height of the disease a case of average severity may be expected to be deeply stuporous with some delirium but without complete coma. A disordered mental condition persists at times well into convalescence. Vertigo or double vision is an occasional complaint.

The bowels are usually constipated. In Goeppert's series diarrhea was not uncommon.

PHYSICAL FINDINGS.—The most important sign of meningitis is *stiffness of the neck* or resistance to flexion. In eliciting this sign the examiner should proceed with all gentleness, especially in the case of children. It is well to secure the history and make other less important and less painful examinations first, in order to gain the confidence of the patient. Rotation of the head from side to side should be attempted, though lateral rigidity is not so significant as anteroposterior. To determine the latter with the patient lying on his back, the hand of the examiner should be inserted between the occiput and the pillow, palm upward, and gently raised. In meningeal conditions this causes pain, and instead of the chin approaching the sternum, there is a tendency for the shoulders to rise from the bed. Unless the condition is marked, one examination is not sufficient, but another attempt to flex the head should be made at the conclusion of the other tests. Unlike a rigidity of less serious import, the neck rigidity of meningitis does not loosen up on manipulation. Netter advises that the naked patient be placed supine on a flat table to detect any spastic arching of the cervical spine.

Though in health the chin should be able to touch or nearly touch the sternum, it is necessary to test for this sign in many non-meningeal cases to appreciate the degrees of voluntary or unconscious non-pathognomonic resistance which may be encountered at different ages and in different patients. In general, by repeated trials at different times one is able to distinguish a true from a false stiffness; but in the early stages of meningitis this may be a fleeting symptom, absent at times. Even with fully developed meningitis, limited to the convexity of the skull (Holt), or in the very young (Koplik), or in patients profoundly prostrated and collapsed, there may be no stiffness. In ordinary cases of meningitis, the rigidity may not be found before the end of the first week, though this is unusual. Needless to say, in cases with general meningococcus septicemia without meningitis or before meningitis has begun, the sign is lacking. Aside from local conditions giving rise to stiffness, such as abscess or neuritis, easily distinguished by the absence of general symptoms, other causes of neck rigidity, particularly meningism, are discussed under Differential Diagnosis. Attempted flexion of the neck in meningitis is usually painful. This is probably the reason for the dilation of the pupils which may frequently be observed when flexion is attempted. The neck sign of Brudzinski is elicited at the same time by flexing the head with one hand, the other exerting counter pressure on the chest to prevent the shoulders from rising; in response to this maneuver in meningitis, the thighs usually flex on the abdomen, and the legs flex at the knees, often with some eversion.

The stiffness of the neck may be so marked that some retraction (opisthotonos) is visible. In the typical developed case of meningitis the posture is on the side so that the head can be more fully extended than when lying on the back. This posture may give a hint of the disease, although a considerable amount of flexion is actually possible on trial. Flexing the back by placing the examiner's arm under the patient's knees and raising them, the patient being on his back, is also likely to demonstrate some painful rigidity. The most marked opisthotonos and retraction of the head is seen in the chronic stages of meningitis, and particularly in the form known as posterior basic meningitis of infants and children.

Of almost equal import with the information obtained by attempting to bend the neck forward, is the phenomenon known as *Kernig's sign;* this is a resistance to passive simultaneous flexion of the hip and extension of the knee. It is best elicited by Osler's method: the patient being flat on his back, the lower leg is raised by the examiner, keeping the tibia horizontal till the femur is vertical; an attempt is now made to straighten out the knee and raise the tibia to a vertical position, the angle of 90 degrees being maintained at the hip. Any limitation of extension to an angle of 135 degrees or less at the knee may be considered as a positive Kernig's sign. In the elderly a positive Kernig's sign is normal and not indicative of disease. In children under two years of age the sign is variable, but with this as with many other reflex phenomena, repeated examination, after having gained the confidence of the infant, will often give information of value. The resistance to extension in a positive Kernig's sign is involuntary and mechanical, due to a hypertonicity of the hamstring muscles, and also voluntary, on account of the pain caused by extension. The sign is at times observed in hip disease and spinal caries, as well as in meningitis and meningismus. Brudzinski's identical and reciprocal contralateral reflexes, a flexion (identical) or extension (reciprocal) of one leg when the other is passively flexed, are frequently present in meningitis, but are not as important as his neck sign.

Other pathological reflexes such as Babinski's and Oppenheim's give no help in meningitis. They may be present, but are usually absent.

A general examination of all the ordinary reflexes is to be recommended, not only for the diagnosis of meningitis, but also for that of poliomyelitis, which often bears a decided resemblance to cerebrospinal fever in the early stages. In general, it is to be expected that the *deep reflexes* will be somewhat *exaggerated at the onset* of meningeal involvement, and the *superficial reflexes dulled*, but changes in the opposite direction may occur, the deep reflexes being usually lost later in the disease. In children, they being the most susceptible to cerebrospinal fever and acute poliomyelitis, one can normally obtain knee, ankle and biceps jerks. The principal superficial reflexes are the abdominal, obtained by stroking either side of the abdomen with a pin or a splintered wooden tongue depressor; the epigastric, a drawing in of the epigastrium when the skin below either nipple is stroked; the lumbar, a contraction of the lumbar muscles in response to a stroking of the skin of the back below the ribs; the gluteal, a similar contraction of the gluteal muscles when the transverse fold of the buttocks is stroked; the cremasteric, obtained by stroking the inner thigh; and the plantar, a flexion of the toes when the sole is stroked, usually accompanied by flexion of the knee and hip. Reflexes are so variable and so subject to volitional control by the patient that any deviation from the normal which is found should be substantiated at a reëxamination. In examining the superficial reflexes, the *tache cérébrale*, a persisting red line with white borders, may be brought out by the stroking, but it is of too frequent occurrence in other febrile disorders to be of any diagnostic value.

A more important sign of meningitis, however, is brought out by the general examination of the reflexes. This is *tenderness,* general hyperesthesia of the skin and deeper structures, which is usually present and significant, if the meningitis is at all severe, and if the patient is conscious. Formerly spinal tenderness was considered as of special importance, but it is now recognized that any or all of the sensory nerves are likely to share in this over-acuteness of conduction. The symptom is commonly attributed to inflammation around the dorsal nerve roots, and to increased tension of the cerebrospinal fluid. Secondary effects of this are the restlessness, apprehension and irritability which the patient shows, a disinclination to be handled or moved. Sophian has called attention to a tenderness at the angle of the jaw in many of the cases.

Corresponding to this exquisite sensitiveness and to the frequent changes in reflexes is a general *stiffness* of the muscles, a hypertonicity often not very definite, but suggestive.

The *photophobia* which is so common in the disease and the sensitiveness to sound are probably likewise due to the afferent nerves being "on edge."

The *pain*, which is primarily cranial, may spread to the neck, back, abdomen, and become generalized. It may be so severe as to make the patient cry out, and frequently contributes to an early delirium.

Sleeplessness from pain, as well as photophobia, may cause a *suffusion of the conjunctivæ.*

Tremor is not uncommon, particularly a coarse intention tremor in children, together with nystagmus.

Actual paralyses are unusual, though strabismus, ptosis and transient face palsies occur in children.

Increased intracranial pressure is not as rapid in development as the other evidences of the disease, but gives rise to a train of signs of which the *tense or bulging fontanel* of infants is the most obvious. Corresponding to this sign in older children and adults is ***MacEwen's sign***, a heightened resonance of the percussion note over the lateral ventricles of the brain (MacEwen, 1893; Wilcox, 1915; Koplik, 1915; Regan, 1918). Though there is disagreement concerning the technic of this sign, a good method of eliciting it is as follows: With the patient's head held on one side, percussion is made by the finger directly on the dependent parietal eminence, or on a point about two inches above and behind the external canthus of the lower eye. When the position of the head is reversed, the opposite parietal region gives the clearer note. To appreciate the increased resonance of a positive MacEwen's, it is necessary to carry in mind the variations due to the thickness of the skull at different ages. Rachitic children may give a clear note also, without increased cerebrospinal fluid. In adults the sign is not as clear, but bony conduction may be eliminated by auscultating the forehead just above the nose while the percussing finger is brought gradually forward from the parietal eminence; if there is increased intracranial tension the note should become less clear as the percussion approaches the stethoscope.

Ophthalmoscopic examination has not given much evidence of value in most epidemics of meningitis. Congestion of the disk is more common than choked disk or optic neuritis.

The *pupils* are usually dilated and react sluggishly. They may be unequal or contracted at first. Hippus, an alternating contraction and dilation independent of accommodation, is sometimes observed.

Deafness is not infrequent in the disease and is often central in origin, as is the blindness which occurs in infants.

The tongue is often dry and tremulous and later becomes covered with sordes. It is very possible that the redness of the throat which has been attributed by some observers to a specific meningococcus pharyngitis is, like the dry tongue, merely a part of the general febrile disturbance. At any rate, sore throat is not a characteristic complaint in cerebrospinal fever.

Retention of urine, probably spastic in nature, is frequent and should be watched for from the first as cystitis and pyelitis are easily induced. Incontinence and dysphagia occur. Polyuria is not infrequent, but albuminuria and glycosuria are no more common than in other fevers. Acute nephritis occurred in 9 out of 161 cases reported by Bourke, Abrahams and Rowland (1915) of the British Expeditionary Force.

The *temperature* of cerebrospinal fever at the onset is typically high, but there is nothing constant or diagnostic in the chart, though *irregularity* is very common. The temperature is a poor guide to the condition or prognosis of the patient.

The pulse is often rather slow in proportion to the temperature, and shows variations independent of the fever. Bradycardia and irregularity are not as characteristic of this disease, however, as of tuberculous meningitis. The blood pressure as a rule is high, especially with increasing intracranial tension; conversely a low blood pressure during the first sixty hours of the disease indicates a dangerous collapse (Fairley and Stewart, 1916).

The respiration in the early stages may not be abnormal, but with fully-developed meningitis, particularly in the later stages and in the severe cases, it is likely to exhibit irregularity (Connor and Stillman, 1912). In children the Cheyne-Stokes type of breathing, with regularly recurring periods of apnea and hyperapnea, is particularly suggestive of meningitis. But the two types most significant are the undulatory irregularity without entire apnea, and Biot's breathing. The latter is of grave prognostic omen. It is characterized by irregular periods of apnea, by constant irregularity in the rhythm and depth of breathing, and by frequent sighing respirations. The respiratory phenomena and slow, hard pulse are both probably due to increased tension of the cerebrospinal fluid, and to the same cause is attributed the fact that death is usually from respiratory failure.

Further examination of the internal organs gives, as a rule, no results of consequence. The spleen is frequently enlarged as in other fevers. Cardiac and pulmonary complications are more often found postmortem than antemortem. The presence of another disease—bronchitis, pneumonia, typhoid fever—by no means excludes meningococcal infection. Jaundice develops in a few cases.

The most frequent skin manifestation of cerebrospinal fever is *herpes,* commonly about the mouth or nose. It does not usually appear before the 3rd day, and is rare in infants under two years of age. In some outbreaks it is rare in any case, but its appearance is a point in favor of this disease as against the other conditions, except pneumonia, which simulate cerebrospinal fever. Herpes has no prognostic significance.

The typical *eruption* of the disease is a hemorrhagic one, the spots varying in size from flea bites to enormous blotches in different cases, and showing much variation in the individual case. This eruption is unusual in sporadic cases, and in many epidemics it is observed in less than 50 per cent. of the cases. Cases with eruption are, on the average, somewhat more severe than those without, but the difference in mortality between the two classes is not constant. The petechial and purpuric blotches appear from the first to the third day, occur on any part of the body, and may be associated with other hemorrhages, bloody bullæ (subcuticular hemorrhages) have been described. Of somewhat later and less frequent occurrence are the eruptions which simulate to some extent those of typhoid, measles or scarlatina. Individual spots will often be found here also to be hemorrhagic. Eruptions, either erythematous or hemorrhagic, are especially frequent over pressure points, such as the elbows and the trochanters. Local flushing alternating with pallor, and localized sweats are part of the vasomotor phenomena. A serum rash, usually urticaria, may be expected in a small percentage of treated cases, but does not commonly appear less than a week after the injection which provokes it.

SPECIAL AND LABORATORY FINDINGS.—1. *Spinal Puncture.*—(*a*) *Indications and Contra-indications.*—The one necessary measure for diagnosis and treatment in cerebrospinal fever is lumbar puncture. On serious suspicion that a case might be one of meningitis, puncture should be performed at once, with serum at hand for administration at the first puncture; each day's delay increases the chances of a fatal termination. But lumbar puncture is not as simple, painless or harmless a procedure as taking a throat culture for diphtheria. What, then, are the indications for its performance?

In the presence of an epidemic, puncture should be done on slighter provocation than in non-epidemic times, both because indefinite illnesses are more likely to be meningitis, and because the cases that occur are more severe and consequently more in need of instant treatment. If cerebrospinal fever is present in the community in more than sporadic intensity—more than one case per week per 100,000 population—all patients with fever of severe sudden onset, headache and vomiting should be punctured. Stiffness of the neck, or Kernig's sign, or delirium, or stupor, or an intense headache, or an eruption which does not disappear on pressure, even though the petechiæ be few in number, is enough to justify the operation, if explanation other than meningitis is not evident. Blood-cultures and nasal cultures should also be made.

The more punctures that are done in a community under those conditions, the lower will be the mortality. In the absence of an epidemic one usually waits for definite signs of increased tension of the cerebrospinal fluid, such as a neck sign or Kernig's sign, in addition to other suggestive findings, before puncturing.

As soon as there is a fair possibility that the symptoms are caused by a purulent meningitis, puncture should be performed. But if the meningeal symptoms are only slight, and the probability is strong that they are due to meningism or poliomyelitis, puncture may be postponed until definite benefit by the relief of pressure may be expected from the operation. The mistake must not be made of refraining from tapping because the first attempt gave negative results, if the symptoms pointing to the meninges continue and increase; the cerebrospinal fluid frequently appears sterile during the early stages of cerebrospinal fever.

The indications in the case of new born and very young infants are different because of the absence of localizing symptoms (Koplik, 1916). It is probable that many cases of meningitis are missed here which either prove fatal early or develop a hydrocephalus. Convulsions with fever not necessarily continuous, restlessness without intestinal disorders, twitching, regurgitation not preceded by feeding, constitute a train of symptoms which justify puncture.

The contra-indications to lumbar puncture are nil, if indications are present and the operation can be performed aseptically. The meningitis division of the New York City Health Department laboratories has performed over 3,000 lumbar punctures, often under the poorest local conditions, without a single secondary infection of the meninges. While there are no contra-indications, the procedure is not to be undertaken lightly in the absence of a reasonable chance that the patient will be benefited. The puncture is somewhat painful and is not without a slight element of danger. Koplik records two sudden deaths on the withdrawal of a small amount of purulent fluid from infants; Flexner and Amoss have shown that an accidental puncture of a meningeal vein may experimentally localize a poliomyelitis virus which would otherwise remain in the blood stream without harm. Weed, Wegeforth, Ayer and Felton (1919) have demonstrated a similar production of bacillary meningitis by lumbar puncture in the presence of an experimental septicemia.

(*b*) *Anatomy and Technic of Spinal Puncture.*—The lower end of the spinal cord in adults is practically always above the third lumbar vertebra and may be as high as the twelfth dorsal. At birth the average level is the third lumbar. The space between the fourth and fifth lumbar vertebræ is therefore always safe for puncture without danger of injuring the cord, and the next space above or below this one can be used. This point of election corresponds usually to the space nearest the line joining the crests of the ilia. It is convenient to mark these crests with tincture of iodin and to paint a narrow transverse line on the patient's back at this level before beginning the puncture. If the back is held properly flexed, the cord is drawn still higher within the vertebral canal, so that one or two interspaces above the three mentioned are safe in adults. The spinous processes of the lumbar vertebræ are practically horizontal, and between the bases of these processes is enclosed a diamond-shaped opening, which is our entrance to the meninges. If the puncture is made in the midline, perpendicular to the plane of the back, as is advisable, the needle will puncture first the skin and subcutaneous tissue, next the tough supraspinous ligament, then the more easily separated intraspinous ligament, then the dura, which is the last resistance to be felt. The total distance traversed varies from one to four inches with the age and with the osseous and subcutaneous development. The subdural space and the arachnoid membrane are negligible; the subarachnoid network containing the cerebrospinal fluid lies practically under the dura. The nerve-roots of the cauda equina are of some importance in lumbar puncture, as they may be slightly irritated or injured, causing symptoms in the lower extremities, bladder or anus. Also, some of the filaments may temporarily cover the open end of the needle, preventing outflow. When the dural resistance has been felt to be overcome, the needle should be pushed no farther, both to avoid any injury to the cauda, and to avoid striking the plexus of blood-vessels in the anterior part of the canal. This plexus is most developed in the dorsal hollows of the vertebral bodies, so that if the needle is in the intraspinous space at an angle of 90 degrees, the point would strike the upper edge of the vertebral body, rather than the vessels. The tips of the vertebral spinous processes are rounded, and in the adult have a tubercle on their lower surface. The needle should therefore be inserted fairly between these palpable tips, but should follow the lower process rather than the spine above. At times the point of the needle will strike the lower spine in this fashion, due to a slight downward inclination of the spinous processes from before backward. This is particularly true if the spine is not well flexed, and may be overcome by directing the needle upward (toward the head) at an angle of not less than 45 degrees. Flexion of the spine does not change the direction of the spinous processes appreciably, but separates them.

If puncture at the first site is to be abandoned on account of nonsuccess or local irritation of the skin, another interspace may be selected, or the lateral method may be tried, the needle being inserted one-half to three inches from the median line and pointed mesially, upward and inward. If only slightly to one side of the midline, the same diamond-shaped opening may be entered as with median puncture, while farther out the needle punctures the subflavian ligament and passes between the sloping laminæ. The disadvantages of lateral puncture are, that the direction is bound to be uncertain on account of the varying thickness of the overlying structures, that the vascular muscle must be pierced, and that the needle tract is longer.

The two most essential points in lumbar puncture are asepsis and the proper holding of the patient. There is more art in the latter than in the performance of the puncture.

No anesthesia is usually employed. A general anesthetic is unwise except for a violently struggling patient, and the possible devitalization of the skin with consequent infection from local anesthesia outweighs its advantage, since lumbar puncture usually is repeated a number of times. Deftness of operation, a due regard for the comfort of the patient, and some mental distraction suffice, and are the safest aids.

Antimeningococcic serum should be at hand for immediate injection without withdrawing the needle in case the cerebrospinal fluid is cloudy at the first puncture. The sterile needles and outfits for gravity administration, which are furnished in commercial packages of the serum, are as a rule very satisfactory. For very young infants a smaller, sharper needle with a syringe for aspiration is sometimes an advantage, but aspiration must be very gently performed, as it is apt to cause bleeding. In infants the prolongation of the thecal sac below the end of the spinal cord is smaller than in older persons. If the pus is very thick or flaky, a needle of larger caliber may be used. If no outfit for administration is furnished with the serum, one may be extemporized by opening and drawing out the lower end of a test-tube so that a rubber tubing about 3/16 of an inch in caliber and 14 inches long may be slipped over it and may be connected at the other extremity with the needle. A bit of glass tubing should be inserted in the rubber tubing near the needle. The needle should be about 4½ inches long and 1/16 of an inch in diameter, with obturator. The bevel of the needle should be as abrupt as is consistent with a sharp point; that is, the distance from the extreme point across the opening at the end of the needle should be as short as possible—not over ⅛ of an inch. The needle, tubing, and test-tube funnel are sterilized by boiling for five minutes. A basin of mercuric bichlorid solution, 1:1000, at a temperature of about 105° F. (40.6° C.), is used for warming the serum.

It is usually advised that the fluid be caught in a series of sterile test-tubes. The author has found bottles preferable, except in cases where but little fluid is to be expected, using short, wide-mouthed, glass-stoppered bottles, of clear glass, about an inch and a half in diameter, and holding one ounce (30 c.c.), the first spurts of the fluid being caught in one and the remainder in others, so that any turbidity due to accidental bleeding will not be present in the last sample. These bottles are sterilized with tin foil or paper caps, can be set down on the edge of the bed or on an uneven floor with little danger of spilling, and are readily transportable. They can be held under the needle in the middle of the bed, if necessary. Theoretically the patient should be brought to the edge of the bed, and the rubber tube be connected with the needle as soon as the fluid begins to flow, but this is not always practical. With these bottles, faint cloudiness of the fluid is more easily detected than in narrow test-tubes—an important point for rapid diagnosis. The amount of fluid withdrawn is likewise readily estimated, and in convenient units, since 30 c.c. is the usual amount of serum in one package.

Sterile gauze and sterile towels should be at hand. The patient's back is cleansed with alcohol, wiped dry with sterile gauze, and the puncture area painted with iodin. The hands of the operator are prepared as for a surgical operation; breaks in asepsis are particularly disastrous because any infection of the spinal canal with pyogenic organisms, other than the meningococcus, is practically always fatal. John L. Morse wears a sterile finger cot over the left forefinger for palpating the intervertebral space to be punctured. One advantage in sterile rubber gloves lies in diminishing the chance of contaminating the hub of the needle over which some of the spinal fluid must flow; every effort should be made to keep the fluid uncontaminated for bacteriological cultures. With care this can be managed by pressing the palm against the head of the obturator and holding the needle with the fingers a short distance away from the hub, or by allowing the fluid to flow through the sterile rubber connection.

Puncture of a febrile patient should not be done in an upright position. The patient should be held by an assistant with the lumbar spine even with the edge of the bed. For successive punctures the patient may lie on alternate sides, although the left side is usually more convenient for the operator. With one arm over the patient's shoulders, the other around the patient's flexed knees, and hands tightly clasped beneath to maintain this posture, the assistant can keep the patient's spine well flexed. A rope made of a sheet may at times serve the same purpose, the assistant's knee being placed against the patient's abdomen to maintain the flexion.

The needle is inserted as previously described, with a straight thrust until the slight resistance of the dura is felt to give way, when the obturator is withdrawn and the fluid allowed to flow. There is usually no harm, and often a distinct advantage, in withdrawing all the fluid possible until the normal rate of flow of from four to eight drops per minute is obtained, but the pressure should not be reduced too suddenly. To obviate this the obturator may be inserted in the needle from time to time, or the rubber tube pinched slightly if this has been connected. If the fluid stops flowing suddenly or fails to start, the obturator should be introduced to clear the lumen, and if that fails, the needle should be reintroduced in a slightly different direction or at a different level. If the fluid is at all turbid, save from accidental bleeding, from 20 c.c. to 30 c.c. of antimeningococcus serum should be inserted—a few cubic centimeters less than the amount withdrawn—even though there is a strong suspicion that the meningitis is due to another organism. The spinal fluid obtained should be guarded against contamination, antiseptics, heat over body temperature, and chilling, and should be taken immediately to the laboratory for bacteriological examination.

(*c*) *Examination of the Spinal Fluid.*—In meningococcus meningitis the fluid is typically under pressure, increased in amount, and turbid with cells which are almost all polynuclear leukocytes. But there are wide ranges from complete macroscopic clarity to pure pus; it is practically always abnormal in amount, or in content, or both. The cellular content may range from about 50 per cu. mm. to hundreds of thousands. A mononucleosis, though unusual, is not inconsistent with meningococcus infection. The one important finding is Gram-negative diplococci, intracellular or extracellular, in smears; these should prove on culture to be meningococci.

Absence of organisms in a turbid fluid is held to be strong evidence of meningococcus infection, because in meningitis due to other pyogenic organisms, such as the pneumococcus, streptococcus or staphylococcus, the cocci are usually readily demonstrable in the first smear. The reverse is rarely true, and the tubercle bacillus, which is notoriously difficult to find in meningeal smears, may cause a slight turbidity.

Bloody fluid probably means that a vessel has been punctured by the needle, but if the blood is evenly distributed it may be due to a hemorrhagic exudate. A yellow fluid coagulating spontaneously (syndrome of Froin) is due to an old hemorrhage.

The chemical tests for albumin and globulin are chiefly of value in differentiating the clear fluid of meningismus from those of poliomyelitis and early meningitis. The albumin and globulin are both increased in cerebrospinal fever.

Fehling's solution in severe cases shows little or no reduction. Prolonged absence of the glucose which is normal in the spinal fluid is an unfavorable sign.

2. *Examination of the Blood.*—The polynuclear leukocytosis of cerebrospinal fever is characteristically high, being over 15,000 in two-thirds of the cases, though cases without leukocytosis are not of great rarity. There seems to be no great prognostic weight to be attached to the white cell count and even in diagnosis practically all meningitides, including many cases of tuberculous meningitis, are likely to show polynuclear leukocytosis.

The presence of the organism of the disease in stained blood films from rapidly fatal cases of cerebrospinal fever has been reported by Andrewes (1906), Coles (1915), Anderson, McNee, Gray, and others (1917), and King (1918). Krumbhaar and Cloud (1918), and Netter and Salanier (1917), found the cocci in smears from the purpuric areas. It may be, as King points out, that search would reveal them in a considerable proportion of septicemic cases, but it is hardly likely, since it is usually necessary to inoculate several c.c. of blood to secure a growth of meningococci.

The frequency of meningococcus septicemia is not settled, but is a question of considerable importance in the pathogenesis and treatment of the disease. Positive blood-cultures were obtained by Gwyn (1899), Salomon (1902), Elser (1905), Jacobitz (1905), Martini and Rohde (1905), Robinson (1906), Marcovich (1906), Andrewes (1906), Davis (1907), Bennecke (1907), Duval (1908), Herford (1908), Liebermeister (1908), Stade (1908), Weiss-Eder (1908), Bovaird (1909), Cecil and Soper (1911), Handa and Nanjo (1913), Mackarell (1915), Bray (1915), Worcester-Drought and Kennedy (1916), Raffaeli (1917), Marie (1917) Pybus (1917), Anderson and others (1917), Thomsen and Wulff (1917) It is noteworthy that the greater portion of these reports are of severe cases. Some of the cases have been of subacute septicemia with meningitis delayed in appearance, or absent altogether. The existence of occasional cases of meningococcus septicemia, or of local meningococcus suppuration, without meningitis, is thus well proven. Recently Herrick (1918, 1, 2, 3) has described from his extensive experience at Camp Jackson a more or less characteristic prodromal stage of meningococcus septicemia before the usual meningitis, and from his laboratory there have been reported two series of consecutive cases showing a high percentage of positive blood-cultures. The first (Baeslack and others, 1918) of 22 cases gave 8, or 36 per cent., positive, of which 50 per cent. died, while 7 per cent. of the cases with negative blood-cultures were fatal. The second series (Herrick, 1918, 3, footnote 2) of 15 cases by Barber and Fleming gave 12, or 80 per cent., positive; the mortality is not stated.

The symptoms described by Herrick for the septicemic stage are malaise, a resenting of interference; frequently coryza, tonsillitis, pharyngitis or laryngitis; apathy, fever, headache, suffused conjunctivæ, petechial rash, asymmetrical deep reflexes, with little or no change in the spinal fluid. Though the uniform existence of such a stage has been a favorite hypothesis of many of the best workers in meningitis, this is the first evidence on a considerable scale in this direction which correlates the clinical with the laboratory findings. Unfortunately the time of appearance of these findings with reference to the positive blood-cultures and to the positive or negative results from lumbar puncture in the series of cases are not given. In an epidemic almost as intense at Camp Beauregard, Maxcy (1918), using a technic similar to Baeslack's, found only one case with positive blood-culture preceding the positive spinal culture out of 27 clinically suggestive patients. It may well be that with improved technic the septicemic stage can be proven for the ordinary non-fulminating case. Elser and Huntoon (1909), using the same ascitic broth dilution method (transplanting to ascitic agar plates) which they found reliable for cerebrospinal fluid, succeeded in obtaining positive blood-cultures in 27 per cent. of 41 cases; but they conclude that these were instances of a transient invasion of the blood-stream, rather than an actual proliferating septicemia demonstrating a hematogenic origin of the disease. The method of Baeslack was somewhat similar. Thomsen and Wolff shook the broth into foam before planting, so as to promote a superficial aërobic growth from the blood. The method used by Barber and Fleming is not given.

3. *Nasopharyngeal Cultures.*—The cultivation of the meningococcus from the nasopharynx, as is done in the search for carriers, was formerly used to some extent for diagnosis where lumbar puncture was refused. But now that the necessity for prompt lumbar puncture and treatment has been shown, as well as the fallibility of diagnosis from nasopharyngeal cultures—since a considerable proportion of the population harbors the meningococcus in the nasopharynx—lumbar puncture or blood-culture should be the only reliance for diagnosis. In case these are negative at the time, the accessory information of a nasopharyngeal culture is of some value. Not all cases of the disease yield a continuously positive nasopharyngeal culture.

Diagnosis.—The one keystone in the DIFFERENTIAL DIAGNOSIS of cerebrospinal fever is the bacteriological examination of the spinal fluid. *Tubercular meningitis* is normally the commonest form of meningitis and may closely simulate meningococcus meningitis, though the onset is likely to be more gradual, the spinal fluid practically clear, with, as a rule, more mononuclear than polynuclear cells; in about 90 per cent. of the cases, tubercle bacilli may be found in the fluid if the search in smears from the fibrin web or from the sediment is careful and prolonged. Results from the inoculation of guinea pigs with the sediment are too slow to be of much service. Pulse irregularities, stupor instead of irritable delirium, and indications of cerebral tract involvement such as Babinski's sign, are more common in tubercular meningitis, but none of these criteria are absolute. (*See* p. 107.)

The *other* primary *purulent meningitides* are only differentiated from meningococcus meningitis by the presence of the organisms concerned, in the turbid spinal fluid. A meningitis occurring in the course of another infection such as a pneumococcus pneumonia or a streptococcus otitis may be due to the meningococcus. Though practically always fatal in a few days, cases of recovery are on record after meningeal infections with the pneumococcus, the streptococcus and the influenza bacillus, as well as with the tubercle bacillus. Not infrequently pneumococcus meningitis shows few of the typical meningeal signs. This may be for two reasons: on account of its predilection for the very young, and because the convexity of the brain may be the only area attacked. Unless there is such a localization, the pyogenic organisms are readily demonstrated in smear preparations from the sediment. A purulent fluid without bacteria usually means meningococcus meningitis, a clear one, under pressure, tuberculous meningitis, poliomyelitis, meningismus or cerebrospinal fever in an early or inactive stage. In many septicemias the organisms are found in the cerebrospinal fluid; a series of five cases of anthrax meningitis has lately been reported by Reece (1917). A relatively benign meningitis may accompany *mumps.*

Poliomyelitis may occur with sufficient meningeal disturbance to simulate closely cerebrospinal fever, but the typical case of poliomyelitis has only a slight degree of clinical meningitis: the children are able to lie on their backs, and there is more stiffness of the lower spine than of the neck. During an outbreak of poliomyelitis there are doubtless many cases of cerebrospinal fever which fail of spinal puncture and proper treatment because they are mistaken for the prevailing disease. The normal prevalence of poliomyelitis in non-epidemic times is about 10 paralytic cases per 100,000 per annum (Leake, Bolten and Smith, 1917, p. 1999; Lavinder, Freeman and Frost, 1918, pp. 66, 86, 87, 97). The spinal fluid of poliomyelitis is typically clear, under pressure, containing glucose and an excess of albumin and globulin, with a cell-count of over 10 per cu. mm. The high cell-count occurs earlier than the increase in globulin and albumin.

The most frequent and most puzzling condition which presents itself for differential diagnosis is the *meningismus* of other febrile infectious diseases. In children particularly, an acute infection with toxemia is likely to produce meningeal symptoms, usually associated with an increase in the amount of cerebrospinal fluid, but almost always without deviation from the normal in its chemical or microscopic characteristics. Pneumonia, scarlet fever, measles, typhoid fever, malaria, also spirochetosis or infectious jaundice, as reported by the French, may thus be mistaken for meningitis. The only safe rule with these, as with the other diseases, is that lumbar puncture and a study of the spinal fluid be made whenever the meningeal symptoms are definite, both for the sake of diagnosis and to relieve the intracranial pressure.

Sunstroke, tetanus, intoxications, influenza, rheumatism, typhus fever, meningeal hemorrhage and renal disease may simulate cerebrospinal fever and require puncture. In children digestive disorders, tetany and spasmophilia can usually be differentiated by a thorough history and physical examination.

Complications and Sequelæ.—The complications of cerebrospinal fever may be due directly to the meningococcus or to other causative agents. Among those of the former class, *internal hydrocephalus* has previously been mentioned. It is caused either by a closure of the median foramen of Magendie and the lateral foramina of Luschka (Key and Retzius) in the roof of the fourth ventricle, preventing the ventricular fluid from reaching the subarachnoid space where it can be absorbed, or by the shutting off and damaging of so much of the subarachnoid space by exudate and adhesions that absorption is hindered. In either case the fluid secreted by the choroid plexus in the ventricles of the brain is under high pressure, producing a bulging fontanel, or a positive MacEwen's sign if the fontanels are closed. It is worthy of note that hydrocephalus may occur with the foramina of the fourth ventricle open, so that lumbar puncture actually yields fluid in abundance, though the absorbing surface of the cerebral arachnoidea is cut off by adhesions encircling the base of the brain (Dandy and Blackfan, 1917). In the presence of actual inflammation, hydrocephalus is practically always accompanied by increased retraction of the head and by Kernig's sign, which may be absent in the chronic hydrocephalus subsequent to the meningitis. Mental deterioration or sudden death is to be feared in latent hydrocephalic cases.

Relapses of cerebrospinal fever after complete convalescence are very uncommon. No case is on record of a second attack of meningitis due to a type of the meningococcus different from that causing the original attack.

Meningococcus septicemia has been mentioned. Metastatic foci not infrequently occur ever in mild forms of the disease. *Arthritis* due to the meningococcus may be single or multiple and is not as serious as to outcome as might be imagined; it must be differentiated from a serum arthritis which may accompany an urticaria about nine days after the injection of serum. In some epidemics meningococcus *conjunctivitis* and meningococcus *epididymitis* are not rare. *Iridocyclitis* seems to have been particularly frequent with the French. Otitis media may or may not be due to the primary infecting organism. Endocarditis with Gram-negative cocci demonstrated in the vegetations has been repeatedly reported, though valvular disease is not to be feared in the recovered cases. Pneumonia may be due to the meningococcus, but more frequently other organisms are found.

Of central nervous disturbances, blindness is more frequent in infants, *deafness* in adults. Localized paralyses occur, and may be permanent, but they are so unusual that unless they are clearly spastic, or unless the meningococcus was demonstrated in the acute illness, the history should be carefully scrutinized to exclude poliomyelitis. Transient facial palsies are not uncommon. Mental defects and epilepsy are much less common following meningitis than is generally supposed.

Of non-meningococcal complications bed-sores and cystitis are particularly to be guarded against; the usual sordes and foul condition of mouth and throat no doubt favor the development of the frequent infections leading from the upper respiratory tract, and of pneumonia.

The necessary treatment of the disease may bring on some untoward results, the more serious of which are avoidable. A certain percentage of the cases may be expected to have a *serum rash*—usually urticaria—from one to twenty days after the first serum injection, and some joint pain and fever may accompany the rash, as is the case with the antitoxin rashes in diphtheria. Unless the patient is naturally or artificially sensitized, these eruptions usually take more than a week to develop; they are relieved by cooling lotions or by menthol ointment. For more immediate anaphylaxis, epinephrin or atropin applied subcutaneously are valuable. The serum may also cause a meningeal reaction lasting about twelve hours, and characterized by an increase in the symptoms, and perhaps by a more purulent spinal fluid—a so-called aseptic meningitis. If the meningococci have disappeared, simple lumbar puncture is indicated under these circumstances. Coming on in the course of treatment, these symptoms are akin to the skin reactions observed particularly during the second week of the Pasteur treatment for rabies. Too rapid injection of serum, or too great a volume, produces a very severe and sometimes fatal condition of shock or collapse. Of course, the appearance of Gram-positive staphylococci in the spinal fluid means that there has been at some time a break in asepsis and that the patient has thereby contracted a fatal form of meningitis.

But aside from organisms introduced at lumbar puncture, mixed meningeal infections are not very rare. Councilman, Mallory and Wright report one case which might have been due to the tubercle bacillus and to the meningococcus. Netter and Salanier report two, Mathers one, and Fitzgerald three cases of pneumococcus meningitis superimposed on cerebrospinal fever. This is of interest as indicating that when the barriers are broken down for one form of meningeal infection, they are weakened for others, and also as indicating the importance of continuing the bacteriological examination of the spinal fluid obtained at each lumbar puncture.

During convalescence from meningococcus meningitis, stiffness and pain in the back, weakness, and a general hypersensitiveness are frequently slow in clearing up.

Clinical Types.—MENINGITIS IN EARLY INFANCY.—The existence of a type of cerebrospinal fever in infants which is difficult to recognize by the ordinary signs has been mentioned under Indications for Spinal Puncture. In their studies on internal hydrocephalus Dandy and Blackfan (1914, 1917) find evidences of meningitis in adhesions throughout the subarachnoid space at the base of the skull, both in cases with a history of meningitis early in life preceding the hydrocephalus, and in cases where the hydrocephalus was said to be congenital and no meningitis was known. They show that the great majority of their cases of hydrocephalus result from meningitis, and justifiably reason that chronic hydrocephalus is to be expected following a meningococcus meningitis only. "That a very mild form of what was probably meningococcus meningitis has been the cause of a number of our cases seems evident from some of the histories, but the illness has been so slight and recovery so prompt that the mother has looked on it as a 'cold,' 'stomach trouble,' or some illness incident to teething, and it is only by careful questioning that the illness is recalled. Yet after these mild symptoms hydrocephalus may result." Lesions exactly similar to those known to have been caused by a meningitis were found in cases with proven congenital hydrocephalus. This opens the question of intra-uterine meningococcal infection and hemic pathogenesis. Cases of meningococcus meningitis with bacteriological verification have occurred within the first few days of life. Doubtless others have died without diagnosis. If any benefit is to be given the new-born cases of meningitis, diagnosis and treatment should be prompt. An otherwise unexplainable sickness, with fever, restlessness and twitching, deserves puncture without waiting for definite meningeal signs. Slight degrees of bulging of the fontanel when the infant is not struggling or crying is important and direct evidence of inflammatory tension. The onset may have been gradual and the neck stiffness, Kernig's sign, or a taut fontanel may not appear until irreparable damage has been done. With the foramina in the roof of the fourth ventricle closed by adhesions (obstructive type), or the absorbing surface of the cranial arachnoid similarly shut off (communicating type), hydrocephalus is bound to occur.

POSTERIOR BASIC MENINGITIS.—It is unfortunate that this has commonly been regarded as a distinct form of meningitis instead of as a sequel of meningococcal infection in the very young. In children below the age of two years, as in early infancy, the onset of cerebrospinal fever is often not definitely meningeal. Cases are likely to go without diagnosis longer than in older children. The purulent meningeal inflammation, not intense enough to cause a rapidly fatal issue, becomes localized particularly at the base of the skull. Even though healing takes place to some extent, the exudate and adhesions either close the foramina of Magendie and Luschka, or encircle the foramen magnum so as to prevent free circulation of the cerebrospinal fluid. Both the inflammatory reaction and the increased tension caused by the lack of outlet for the secretion of the choroid plexuses produce the reflex retraction of the head which is so pronounced a feature. Emaciation becomes extreme and the spastic bowing backward of the trunk with hyperextended extremities, infolded phalanges, and upturned eyes forms a distressing and all but hopeless picture. The course of the disease, almost always fatal in this stage, averages six to eight weeks, while the average duration of tubercular meningitis is two and a half weeks; as a rule, cerebrospinal fever is the only meningitis of bacterial origin which is not fairly rapidly fatal.

MILD CASES.—Though the mild cases may begin very acutely, the somewhat more gradual onset is more frequent in this than in other non-infantile forms. These are the cases which would recover without lumbar puncture or specific treatment, and which distinguished cerebrospinal fever formerly as "That meningitis from which recovery may occur." In general, the onset is similar to that of the ordinary acute case, but after the stage of invasion, improvement definitely sets in and continues.

Whether truly "abortive" cases occur in any number, in the same sense in which we describe "abortive" cases of poliomyelitis—that is, mild cases without the specific localization—is a moot question. Some eminent European epidemiologists (Hirsch, 1866, 1886; Bruce Low, 1916) give credence to reports of large numbers of ambulant, abortive cases. All admit that the type of the disease may vary considerably in different outbreaks. Except possibly in the recent experience at Camp Jackson, the greater number of proven generalized cases with positive blood culture but negative spinal fluid have been severe cases. Occasional mild cases have been reported of definite localization outside of the meninges. It is very possible that failure to demonstrate such mild general infection in the past has been due to the fallibility of our blood-cultural methods, with such a delicately growing organism as the meningococcus. Another explanation may be that the Camp Jackson epidemic was somewhat unusual in its proportion of definitely septicemic cases. Despite investigations made to that end, it usually happens that no more cases of indefinite illness, meningism, or "influenza" are observed among those who are isolated as carriers of the meningococcus than would be expected in an indiscriminate group. Analogy with other diseases gives every reason for the belief that such abortive cases of cerebrospinal fever occur; but that their number is generally large is still undemonstrated. For practical purposes, a case of cerebrospinal fever should be expected at some stage of the disease to show definite signs of meningitis, such as a degree of neck rigidity, Brudzinski's or Kernig's sign. During epidemic times, it may frequently be wise to administer serum intravenously and intraspinally before these signs appear.

ORDINARY ACUTE CASES.—After the usual acute onset and twenty-four hours or more of increasing symptoms there is not infrequently a stationary period or slight remission. The signs pointing to the meninges may not be clear for one or more days. Even if the primary lumbar puncture is unfortunately delayed beyond the first day, a relatively clear fluid may occasionally be obtained, though in the thirty cubic centimeter bottle some slight cloudiness can usually be detected in the earliest punctures. Under proper active treatment these cases may be expected to improve, though not without relapses, so that the spinal fluid is free from meningococci in one to three weeks, and the symptoms gradually subside. Kernig's sign and some neck stiffness are among the last symptoms to disappear. If the case is progressing favorably, glucose should appear in the spinal fluid after a few days of treatment, so that Fehling's solution is reduced to a degree approximating that in normal fluids.

In spite of treatment some cases of this group will persist to a chronic stage, and some will go on to an acutely fatal termination within a week.

Subacute and Chronic Types.—The more protracted stages may be divided into those in which the persisting infection is the overshadowing picture, and those in which hydrocephalus is predominant. Meningococcal meningitis is by nature relatively mild, since it is the only bacterial infection of the meninges, recovery from which occurs spontaneously in any considerable number of cases. There are cases,therefore,in which the bodily defenses, with or without specific therapy, are nearly able to overcome the infection, but in which the organisms, protected from entire elimination, are able to prolong and renew the fight until the exhaustion of one side or the other determines the issue. If serum treatment is used this may occur either because the variety of meningococci is resistant to the particular serum employed, the pus sometimes becoming too thick to flow through the needle, or because the pus is localized in pockets which are not adequately drained, and which the serum does not reach. In such cases the symptoms of the acute stage are prolonged, often with remissions of greater or less degree; irregular febrile exacerbations with emaciation, stiffness of the neck, Kernig's sign, and a semi-delirious stupor are prominent in these stages. In the less purulent hydrocephalic cases, the fluid obtained at successive lumbar punctures gradually clears, then becomes decidedly lessened in amount, till practically dry taps occur. Coincidently the symptoms are aggravated, particularly headache and opisthotonos. The condition is akin to the posterior basic meningitis of the very young.

Hyperacute and Fulminating Cases.—These cases are even more characteristic of epidemics of cerebrospinal fever than are the posterior basic cases characteristic of the sporadic appearance of the disease. The occurrence of even one of these rapidly fatal cases should be enough warning to put an entire community in readiness for an outbreak by securing ample supplies of serum and providing every facility for rapid diagnosis and treatment. The most intense cases may be fatal within four to twenty-four hours of the first known symptoms; sometimes they are overwhelmed by the infection before clearly localizing symptoms have appeared. The patient retires after a day of customary activity and is found in a coma in the morning, or falls down in the street. Perhaps a hemorrhagic eruption, appearing before death, gives a clew to the true disease, though external evidence of meningitis is lacking. The symptoms are those of collapse. In other cases malaise, headache, vomiting or a chill may precede the unconsciousness by a few hours, and some stiffness of the neck or a Kernig's sign be found before death, which occurs from one to three days later. Purpuric eruptions are especially frequent in the very severe cases, though different epidemics vary widely in this respect, as well as in the relative number of such hyperacute cases. It is particularly in the earlier part of a local epidemic that one expects the most foudroyant cases, and the number of deaths within twenty-four hours of the onset is always small.

As has been mentioned, the fulminating purpuric cases are more likely to yield positive blood cultures than are the ordinary type, yet even here spinal puncture is usually positive. If the spinal fluid and the medium are kept at body temperature, and if the medium is properly prepared and is used while moist, meningococcus colonies appear; the diplococcus can also usually be demonstrated in stained smears from the centrifuged sediment. It is astonishing how early in the disease the cerebrospinal fluid may be frankly purulent.

Treatment.—PROPHYLAXIS.—*General Protective Measures.*—Bed-side prophylaxis is important in all cases, whether an epidemic is present or not, on account of the possible, though remote, danger from the individual case. Intimate contact with the sick and with his associates should be avoided as far as possible; one, at least, of the latter is a carrier. In a hospital ward, where other diseases are being treated, the beds should be spaced at least eight feet apart and adequate ventilation maintained. In cramped quarters much can be accomplished by "staggering" the beds, so that the foot of one bed intervenes between the heads of two others.

Meningitis is in general no more contagious than typhoid fever or pneumonia. Secondary infections in one household are unusual, but for all infectious diseases contracted by way of nose or mouth, **aseptic nursing** should be enjoined. After caring for the patient, the nurse should wash her hands in an antiseptic solution, and all persons should avoid a zone of six feet from the patient when the latter is coughing or phonating. Visits from relatives and friends are unnecessary and may be harmful even in non-epidemic times. The discharges from the patient should be disinfected if not deposited directly into the sewer. In general, the meningococcus can be counted upon as a quickly dying organism, the danger lying in apparently well carriers, and not in inanimate objects or prostrated patients. **Hexamethylenamin** (urotropin) in 5 to 15-grain doses (0.3 to 1.0 grams) may be given to prevent an infectious cystitis, and also to destroy the meningococci excreted in the urine. It probably has no effect on the meningeal infection (Burnam, 1912).

Notification.—The local health office should be notified by telephone immediately upon suspicion of meningitis, in order that the public may have an early preparation for a possible epidemic, and in order that any laboratory or diagnostic facilities may be placed at the disposal of the physician and patient within twelve hours. Prompt notification of each case to the health authorities enables general measures to be taken at the time when needed. In the presence of an epidemic, these general measures should be carried out, their extent varying with the apparent danger, and with the necessities in each instance. Unnecessary contact among the public at large is to be discouraged—the means of least necessary and of most promiscuous contact being barred first.

General nasopharyngeal cultures were undertaken in the British Army, and a carrier rate of 20 per cent. was considered dangerous, necessitating the **spacing out of the men,** and other measures to reduce contact. The culturing of all those in more or less contact with actual cases was undertaken in the British and also in the American Army and Navy. In the British Army in England those men were isolated who were found to be carriers of one of Gordon's four epidemic types of meningococcus. In the English Navy at Portsmouth (Fildes, 1918) all new entries were swabbed, all close contacts (about six men to each case) were swabbed twice, and all other messmates of each case of cerebrospinal fever had one culture taken. If any of these were positive, four negative cultures at weekly intervals were required before release. This necessitated three isolation camps, one containing those men on whom report had not been made, a second for those found to be carriers at the last examination, and a third for those found negative at the last examination, pending the fourth negative culture for release. Under such a system it was evident that the number to be isolated would depend upon the number cultured, irrespective of any connection with cases of the disease, and also upon the time and pains spent on the individual cultures and upon the number of negative cultures required for release, since men giving one, two or three negative cultures were not uncommonly found positive at the next trial. The number of colonies to be picked from a plate has also a bearing on the number of carriers found (Vines, 1918). The handling of such a campaign requires not only very competent bacteriologists with good facilities, but also an organization for the isolation of five per cent. or more of those swabbed. Leishman (1918), Mink (1918) and Short (1918) seriously question the advisability of such a procedure. On the other hand, in American camps where the carrier campaign was inaugurated promptly, the meningitis rate appeared to fall more quickly than in the others (Russell, 1918). Even the scientific opponents of Gordon's classification admit that his procedure diminished the spread of the disease (Walker, 1918). In a civil community the search for carriers and their quarantine involves either the missing of such a large proportion of the carriers, or the isolation of so many healthy individuals, as to be impracticable. Attention should rather be directed toward diminishing opportunities for close contact among the population as a whole during an epidemic. There is no means, such as the virulence test in diphtheria, for determining which of the carriers are dangerous.

Individual Prophylaxis.—One definite cause of increased susceptibility may be removed by the **avoidance** of undue exposure to **cold** and to **fatigue.** Various sprays, douches and inhalations have been used to rid the nasopharynx of meningococci and to prevent infection. As ordinarily applied, these can have little if any effect. The localization of meningococci in the folds and recesses of the mucous membrane would necessitate such vigorous application or such strong concentration that the general use of these methods would be out of the question. Cleansing of the throat by **bland washes** is to be recommended.

The wearing of **masks** by attendants on the sick during epidemics has experimental evidence in its favor, as regards the transfer of bacteria. Such masks should be at least six to eight ply and should be shaped or marked so that the same side is always worn next the face.

Indiscriminate **vaccination,** with suspensions of killed meningococci, has been urged, but there is no proof that meningococcus vaccine has any protective value against natural infection in man; the analogy with typhoid fever and the possibility of the demonstration of antibodies in the blood of the vaccinated have been considered grounds for the practice. On the other hand, we know that meningitis will develop in spite of such vaccination, and since a vaccine powerful enough to develop efficient immunity may do more harm than good, it would appear wise to concentrate effort on the known valuable field of providing prompt diagnosis and proper treatment of the cases as they occur, until it be shown that vaccination is efficient.

GENERAL MANAGEMENT.—The patient's bed should be placed in a **room** as **quiet** and as well **isolated** from the rest of the house as possible. There is probably no acute non-surgical infection, save laryngeal diphtheria, in which **hospitalization** is of as great advantage to the patient as in cerebrospinal fever. For purposes of quarantine, as well as for instant expert medical and nursing attention, and for ready laboratory facilities, a hospital, if properly equipped and available, is to be advised. This is in spite of the fact that most acute infections conveyed through the respiratory tract do better at home than in hospitals. Fluids should be pushed, some liquid being given at hourly or half-hourly intervals when awake. Mouth and throat asepsis requires constant attention, as in typhoid fever.

Diet.—When the vomiting has subsided, the **diet** should be made very **liberal.** Though the fever interferes with the digestion of any but the simpler foods, these should be made as varied and as palatable as possible, in order to maintain the nutrition. Forced feeding may be necessary when a tendency to chronicity develops.

SYMPTOMATIC TREATMENT.—The primary symptomatic indication is the relief of pain and sleeplessness. Though **bromids, hypnotics** or other analgesics should first be tried, the severe headache of cerebrospinal fever usually requires **morphin** unless relieved by lumbar puncture. The meningeal serum reaction often intensifies the headache for a few hours. Since the disease is by no means devoid of the danger of a terminal pneumonia, the depressant should not be pushed or used as a routine, but each dose given according to the indications, in order to gain some sleep for the patient during the twenty-four hours. **Sodium bromid** 1.0 gram (15.5 grains) t.i.d. may partially relax the muscular hypertonicity and act as an adjuvant to the opiate whenever the latter is necessary. **Catheterization** may be necessary for a short period, but the urinary output should be watched from the first, and other means of relaxing the bladder sphincter used if possible. **Cathartics** or **enemata** are usually required for the bowels. *Cardiac stimulants* are rarely advisable. Some English Army officers have used **epinephrin** intravenously or intramuscularly in pulseless fulminating cases with apparent success, giving it in 0.6 to 1.2 c.c. (10 to 20 minims) doses every four hours according to the pulse (MacLagan and Cooke, 1917). It would obviously be dangerous in the slightly later stage of increased cerebral tension and heightened blood-pressure.

SERUM TREATMENT.—The method of **lumbar puncture** has been described (p. 98). This in itself is distinctly helpful, relieving the cerebral pressure, withdrawing purulent fluid and, possibly, permitting the formation of more antibacterial exudate, though there is no experimental evidence for this last. However, its former chief advocates have been ready to admit that the results with lumbar puncture alone were poorer than those obtained by the combined use of *drainage* and a potent *antimeningococcic serum* (Dunn, 1911; Netter, 1911; Foster, 1918). But the serum must be introduced at the site of the chief infection, that is, intraspinally, in the subarachnoid space. This necessarily limits the amount that can be given at one time, and prevents the early, intensive application of the antiserum at one dose, as is most successful in diphtheria.

As mentioned previously, lumbar puncture should be performed on suspicion of meningitis, and **antimeningococcic serum** injected at once if the fluid is at all cloudy, without waiting for bacteriological examination. This should be done even with a clear or blood-tinged fluid, if the history is suggestive, and if other cases are occurring. The amount to be injected should be less than that removed. It is safer to give another injection after from eight to twelve hours than to increase the intraspinal pressure by giving a greater amount at the first injection, causing thereby not only pressure symptoms, but a heightened toxic action of the necessary preservative in the serum.

The routine dose is from 20 to 30 c.c. It is safe to go above the latter amount when a very large amount of serum has been withdrawn, and when prior injections in the same patient have been borne without depressant reaction. The injections should be made very slowly, by gravity, the serum having previously been warmed to a few degrees above body temperature. Sophian advises the use of a sphygmomanometer during injection, and the stopping of the serum if the total fall in blood-pressure reaches 20 mm. Due probably to the elasticity of the tissues in children, they can be given practically as large doses as adults, and even in infants the doses are much greater than in proportion to the body weight. Some discomfort is often noted toward the end of the injection, and this, if very severe, is a signal for stopping. Since the amount which can safely be injected is limited, however, every effort should be made to allow this to be maximal, by withdrawing as much fluid as possible previously, and by proceeding with the injection gently and carefully. At the conclusion of each injection, the foot of the bed may be raised six to eighteen inches for three hours, to allow the serum, which is of higher specific gravity than spinal fluid, to gravitate toward the cerebral meninges; for three hours before puncture the head may similarly be raised to facilitate the denser exudate seeking the subarachnoid interstices of the lumbar region.

Injections should be repeated daily until no meningococci can be found in the spinal fluid, or for four days at least, if they disappear earlier. If the case is a very mild one, fewer than four will suffice, but even though improvement is marked it is not safe to stop short of overwhelming the infecting cocci as rapidly as possible, in order to prevent the development of "serum-fastness" by the microörganisms, and relapses. Frequently, more than four daily injections are needed, but if symptoms have ameliorated by that time, and if the spinal fluid has cleared to a considerable extent, an interval of forty-eight hours may be permitted to elapse. The serum itself provokes a meningeal reaction which may be severe at times, with headache, pain and more marked retraction for eight hours or more, and this may be reflected by increased cloudiness in the spinal fluid. In order to differentiate this from an infection with a few organisms not growing in cultures, or not seen in smears of the sediment, it is well not only to omit injection for a day or two after the first intensive series, but to perform **lumbar puncture without serum** as a routine toward the end of the treatment. As long as meningococci are readily demonstrable in the spinal fluid, intensive serum treatment is indicated; and if the infection does not yield to eight or ten injections of one serum, another should be tried, preferably a serum which has been matched against the strain of meningococcus obtained from the particular case in question.

If the first intensive series of daily injections has been completed, and meningococci are again found in the spinal fluid, another series of at least four daily injections should be given. The total number of injections necessary may exceed fifteen or twenty.

In very severe cases, valuable time may be saved by giving more than one injection in twenty-four hours, but this advantage is to be weighed against the disadvantage of continuing the possible meningeal reaction from the serum. Josephine Neal, in her large experience with sporadic meningitis in New York City, advises against the more frequent injections. During a highly fatal epidemic and with an alert meningitis hospital service, the eight- or twelve-hour injections are indicated at times.

In case there is prior evidence of severe meningeal infection, and the symptoms persist or increase, but no fluid is obtainable on repeated lumbar puncture, the situation is indeed desperate. One "dry tap" should not prevent repeated trials; bits of exudate or tissue may plug the needle, or the pus may be too thick to flow. Larger and sharper needles should be tried at different levels. The lateral as well as the median route should be used. If under these conditions little or no fluid is obtained, one very possible inference is that the lumbar region is occluded from the secreting ventricular plexuses—most frequently by beginning adhesions in the region of the fourth ventricle, or lower in the vertebral canal. To break these up, Herrick advocates Cobb's device of forcible manipulation of the neck under inhalation anesthesia; this may be followed by a free flow. It is not safe to sit the patient up, and fatal accidents have even followed forced coughing in order to start the flow. Surgical procedures for these obstructions are mentioned below.

In Great Britain and on the continent **lavage** of the spinal space has been performed with saline or with an antiseptic solution. This is *more dangerous than beneficial.* Flexner and Amoss (1916) have shown that many antiseptics actually retard recovery by inhibiting phagocytosis in the spinal fluid.

Fresh normal or convalescent human serum was tested experimentally and injected intraspinally in human cases with varying success by Davis (1907) and by Mackenzie and Martin (1908); it was added to ordinary antimeningococcic serum as complement by Fairley (1916) in Australia, and by Kolmer (1918) in Philadelphia. Although this procedure is theoretically sound, its use was abandoned in Australia, probably both on account of its cumbersome technic and the danger of non-sterility, and because the plain antimeningococcic horse serum used intensively, well controlled bacteriologically, with a lumbar puncture squad watching the patient practically every hour of the twenty-four, gave even more satisfactory results. (*See* p. 117.)

The **intravenous** use of antimeningococcic serum has been practiced from time to time (Nowland, 1916; Stewart, 1917), on the ground of the systemic nature of the meningococcal infection, and it has recently been strongly urged by Herrick and his coworkers. Too little attention has doubtless been paid to this in the past, but it cannot be denied that most cases of cerebrospinal fever, as they come to the attention of the physician, are overwhelmingly meningeal; it is in the meninges that the battle must be fought and won. In very early and obviously septicemic stages the large doses of from 50 to 120 c.c., advocated by Herrick, should be given intravenously, with the precautions observed in serum injections for pneumonia. Even though only minimal amounts of antibodies reach the cerebrospinal fluid from the blood, the excretion of antibodies from the spinal fluid into the blood stream may possibly be retarded by raising the antibody content of the latter. The serum has also been used with success locally, in joints and in other purulent, meningococcal foci; but the arthritis of cerebrospinal fever tends to recover spontaneously.

SURGICAL INDICATIONS.—The most frequent, grave condition for which **surgical intervention** is suggested is internal hydrocephalus, due to a stoppage of the outflow of ventricular fluid. This is probable when little or no fluid is obtained at the lumbar puncture, in spite of headache, with vomiting irrespective of the taking of food, with increasing blood-pressure, nystagmus, dilated sluggish pupils, a slight or considerable bulging of the fontanel in an infant, or with a developing MacEwen's sign in an adult. Optic neuritis, slower pulse rate, increased head retraction might be expected but are very frequently absent, and wasting, impaired mentality and sphincter trouble come too late to be of great help in diagnosis.

In an infant the signs first mentioned are indications for **puncture of the fontanel.** Zingher (1919) believes that persistent dry taps, with slight bulging of the fontanel, when the infant is not crying or struggling, are sufficient evidence for cranial puncture. This may be done with a needle similar to that used for lumbar puncture; the head should be shaved without abrasion, and tincture of iodin applied to the site. The infant is held firmly wrapped in a blanket, one assistant maintaining the head in exact position. Any lateral motion of the needle is dangerous. The sterile needle is inserted at an outer angle of the fontanel, not less than 1 cm. from the median line, to avoid the longitudinal sinus, and pointed very slightly forward. If the site chosen is over 2 cm. from the median line, the needle should also be directed inward at an angle of not more than 20° from the perpendicular; if it is only 1 cm. from the median line the direction should be slightly outward. When a depth of from 2 to 5 cm. is reached the obturator is withdrawn to allow the fluid to flow. The needle must be held very gently, to prevent lateral motion. Serum may be administered as by lumbar puncture. At successive punctures alternate ventricles should be drained, and lumbar puncture be performed at a later date, to ascertain the reestablishment of the spinal "circulation." Despite the apparent simplicity of this procedure one cannot escape the impression that the successful cases are reported and many unsuccessful ones unrecorded. Certainly in adults ventricular puncture should be performed only when a personnel is available, which is expert in the strict asepsis of brain surgery. Puncture through the corpus callosum (following the falx cerebri), or frontal, temporal, or occipital **trephining**, may be used. Continental surgeons have not hesitated to puncture at the lower cervical vertebræ, and along the roof of the orbit through the sphenoidal foramen (Dopter, 1918), when there seemed to be a stoppage above the lumbar site. Haynes advocates drainage of the cisterna magna.

By persistent **lumbar puncture,** with serum injection when indicated, some cases of apparent internal hydrocephalus have been cured. On the other hand, it is by early diagnosis and prompt treatment of internal hydrocephalus that good results may be hoped for.

Enucleation may be needed for panophthalmitis, and **paracentesis** for otitis media.

Treatment of Complications and Sequelæ.—In this wasting disease special care must be taken from the first, and as a routine, to **prevent bed-sores. Alcohol and powder** on the pressure points and clean, smooth sheets are necessary.

The treatment of hydrocephalus has been mentioned.

The itching serum rashes of the later periods of the disease may be relieved by an evaporating **lotion** such as:

Chlorali hydrati	10 grams (2.5 drams)
Phenol	2 grams (0.5 dram)
Aq. camphoræ	125 c.c. (4.25 fluid ounces)
Alcohol	125 c.c. (4.25 fluid ounces)

or by 5 per cent. **menthol ointment.** The rare cases of collapse immediately after serum treatment should receive **adrenalin intravenously** in 1 c.c. (16 minim) doses.

Joint complications usually take care of themselves, with local applications, but may require puncture and serum injection. Therapeutic measures directed against gonococcal conjunctivitis are effective against the meningococcal form, but the more serious ocular conditions start as iridocyclitis, or even deeper in the eye, and may advance very rapidly.

Convalescence.—The subsidence of fever and acute signs of inflammation are usually followed by stiffness, persistent Kernig's sign and by various pains. **Massage** and gentle, **passive exercise** aid in restoration, and do no harm. Restoration to full vigor and activity is frequently very slow, and the patient should be guarded against undue exposure or strain. A degree of internal hydrocephalus may persist, and cause a rapidly fatal issue, without persistent infection, but with the clinical symptoms of relapse.

Prognosis.—As to Recovery.—Just as various outbreaks of the disease differ widely in their symptomatology, some being for example largely eruptive and purpuric, while the nervous symptoms predominate in others, so the case mortality rate varies greatly. The Silesian epidemic of 1905, before serum treatment began, had a mortality of 58 per cent. among 3,102 cases (Westenhoffer, 1906). The small 1917 Copenhagen outbreak (Thomsen and Wulff, 1917) had practically 100 per cent. mortality. Sporadic cases in general have a lower fatality than epidemic cases, and the later cases are usually milder than those occurring during the first part of an epidemic. The best body of statistics of serum-treated cases is that of 1,294 collected by Flexner in 1913, showing 18.1 per cent. mortality among those in which the treatment was instituted during the first three days, 27.2 per cent. for those in which it was begun on from the fourth to the seventh day, and 36.5 per cent. for those in which serum was first given after the seventh day; only a small number who died less than twenty-four hours after the injection have been excluded. Some small series have given a mortality rate below 10 per cent.

The most encouraging point in favor of the serum treatment is the evidence that the mortality decreases in proportion as the patients are treated earlier in the attack; all statistics agree on this. The figures are not comparable to those of diphtheria as best treated, but cerebrospinal fever without serum is a more fatal disease than diphtheria without antitoxin. The difficulties in the way of proper treatment, by reason of the need of continual injections, are also much greater. As the medical profession becomes more adept and more persistent in the treatment, we may expect the mortality to fall. Promptness, persistence and proper technic are nearly as important as the proper serum, but in two instances, in Australia, non-specific horse serum was used on a series of cases, from lack of antimeningococcic serum, with disappointing results (Sandison, 1916).

As an indication of what may be expected with good treatment of sporadic cases, usually outside of hospitals and in congested parts of the city, the following tables from Neal may be quoted:

MORTALITY IN CEREBROSPINAL FEVER: By years

	Total Number of Cases	Patients Recovered	Patients Died	Results Unknown	Mortality Per cent.
1910–1911	17	10	7	0	41
1911–1912	24	7	14	3	66
1912–1913	30	17	12	1	41
1913–1914	41	28	13	0	31.7
1914–1915	38	25	13	0	34
1915–1916	57	40	17	0	29.8
1916–1917	85	65	20	0	23.5
1917–1918	112	90	22	0	19
1918–1919	78	62	16	0	20.5
1919–1920	36	18	18	0	50
1920	19	18	1	0	5.3
Totals	537	380	153	4	28.5

MORTALITY IN CEREBROSPINAL FEVER: According to age

Age	Cases	Mortality Per cent.
Under 1 year	102	46
1 to 2 years	46	31
2 to 5 years	89	16.8
5 to 10 years	108	25.9
10 to 20 years	84	23.8
Over 20 years	80	31

MORTALITY IN CEREBROSPINAL FEVER

According to time of beginning treatment

Time after Onset	Cases	Mortality Per cent.
1 to 3 days	200	23.5
4 to 7 days	137	27.7
7 to 14 days	63	37
2 to 3 weeks	47	47.8
Over 3 weeks	22	40.8

It is to be expected that in epidemic periods the mortality in cases seen within the first three days would be reduced below that indicated above for sporadic cases, because in non-epidemic times cases which are not of the very severe type are likely to be misdiagnosed at first and the treatment thereby delayed.

MODE OF DEATH.—The early deaths commonly occur from cardio-vascular failure, with very low blood pressure. Respiratory failure is the usual cause of death, if the first shock of attack has been survived. The cerebral congestion and the internal hydrocephalus both raise the blood pressure, and the respiratory center bears the brunt of the attack, as is evidenced by the irregular respirations. A blood pressure consistently below 120 mm. in the first 60 hours, or above 120 mm. thereafter, is of serious prognostic import. In the chronic stage, death may come from pneumonia (as also in the acute stages), or from malnutrition and exhaustion. (*See* p. 96.)

AS TO DURATION.—Cerebrospinal fever is probably the most generally variable of any infectious disease as to duration. The symptoms in fatal cases may have an observed length of four hours, or of months. Hardly any other diseases met with in this country will kill as suddenly, and with as little evidence of localization, as do cerebrospinal fever and acute poliomyelitis. Flatten (1906) recorded 7.5 per cent. of fatal non-serum-treated cases as dying in the first twenty-four hours, the same number in the second, 24 per cent. in the first three days, 24 per cent. from the fourth to the seventh day, 52 per cent. later than the seventh day, and 7 per cent. after eight weeks or more. Serum-treated cases usually either die early or survive; sudden cessation of symptoms is frequent. This indicates that the problem is to get the serum into the spinal tissues promptly and adequately. So much depends upon the thoroughness of administration of the serum, and upon promptness of diagnosis, that figures as to the length of the convalescence are of little value. (*See* pp. 107 and 108.)

AS TO FUNCTION.—With serum treatment the paralyses and mental deteriorations, which were formerly supposed to follow meningitis in a large proportion of cases, are very few. It is not improbable that many of the paralyses assigned to meningitis were due rather to poliomyelitis. Deafness unfortunately occurs early, often before treatment is instituted, and is still frequent; prompt diagnosis and treatment is our only hope of reducing the incidence of this permanent disability.

Pathological Anatomy.—The earliest anatomical change is a hyperemia of the pia and arachnoid over the brain and spinal cord. Some clouding and edema of these tissues next appear, and faint yellow patches may be visible in places. Microscopically this is seen to correspond to an infiltration with polynuclear leukocytes. Frank pus may then be found, which in the chronic stages becomes fibropurulent, and organizes into adhesions and thickened meninges. The exudation is most prominent along sulci and around vessels; the base of the brain and the posterior surface of the cord are the chief sites of deposits, but the purulent infiltration usually extends up around the lateral surfaces of the cerebrum, sparing in general the longitudinal fissure, and is abundant over the upper surface of the cerebellum. Collections of pus are found at the roots of the cranial and spinal nerves.

The spinal fluid coincident with these changes is at first nearly clear, then cloudy, and may become actual pus. The cells of the exudate are largely pus cells, but lymphoid and plasma cells may be found in the tissues toward the periphery of infiltrates, and very large cytophagocytic cells are also found. These latter have been described by Councilman, Mallory and Wright as originating from connective tissue cells or from cells lining the lymph spaces. The proliferative endarteritis common in tubercular and pneumococcus meningitis is unusual in this disease.

The ventricles of the brain take part in the process, the subependymal and choroid vessels are injected and the ependyma raised or displaced by edema. The ventricular fluid is cloudy, but does not uniformly correspond with the spinal fluid. Particularly if the collections of pus or adhesions have impaired the free passage of fluid through the foramina of Magendie and Luschka (obstructive hydrocephalus), or if the cerebral meninges have been blocked off by adhesions surrounding the foramen magnum (communicating hydrocephalus), the ventricles are dilated.

The meningeal inflammation frequently extends down into the cortex of the brain, less often into the spinal cord; and cellular infiltrations, not always apparently limited to the periphery of vessels, are found here. Hemorrhages into the nerve tissue also occur, and areas of softening may coincide with paralyses. The cranial and spinal nerve-roots show inflammation and infiltration, and extension of the process along the eighth nerve or along the optic nerve may give labyrinthine deafness or a purulent panophthalmia. Meningococci are found intracellularly and extracellularly in the exudate, more especially in the acute rather than in the chronic stages. The meningococcus also gives rise to a bronchopneumonia, dense enough at times to resemble lobar pneumonia clinically and macroscopically. In such cases meningococci are found in enormous numbers in the pus cells of the pulmonary exudate. Croupous pneumonia as a complication of cerebrospinal fever is due to the pneumococcus. The spleen is enlarged, but not as regularly as in other infectious diseases.

Historical Summary.—The first record of an epidemic of meningitis is that of Vieusseaux, who described an outbreak in Geneva, Switzerland, in the winter and spring of 1805. Doubtless epidemics had occurred before this, but the accounts are dubious, and sporadic cases could not be distinguished from other meningitides. In 1806, without having heard of the Swiss outbreak, Danielson and Mann described an epidemic in Medfield, Massachusetts, with five postmortem examinations. From that time we know of hundreds of epidemics throughout the civilized world. The division into epidemic periods made by German writers is more or less artificial, though it is evident that even countries such as the United States, in which epidemics are particularly frequent, have been practically free from serious outbreaks, as far as the records go, for years at a time. In France the greater part of the earlier epidemics were among the troops.

The bacteriological history of meningitis begins with the demonstration of the meningococcus in 1887 by Weichselbaum of Vienna. The importance of this discovery was discounted for a number of years by the confusion of the meningococcus with the pneumococcus and other Gram-positive cocci (Jaeger), until such researches as those of Councilman, Mallory and Wright, which were made during the Boston epidemic of 1897, established the correctness of Weichselbaum's original descriptions. In the Portuguese epidemic of 1901–1903, Bettencourt and França found the organism in every one of 271 cases investigated. In 1901 Albrecht and Ghon first showed the presence of the meningococcus in the nasal secretion. The Silesian epidemic of 1905 comprised 3,317 cases and furnished the material for von Lingelsheim's thorough bacteriological work. This epidemic lingered till the Rhenish-Westphalian outbreak of 1907, and these, together with the New York epidemic of 1904–1905, instigated the preparation and use of the serums of Jochmann, Kolle and Wassermann, and that of Flexner. One of the most extensive recent epidemics, aside from those coincident with the concentration of troops for the war, was that of 1911–1912 in the southwestern United States.

NEW BIBLIOGRAPHY

Evans, A. C. The tropin reactions of Antimeningococcic Serum, 1920: Hygienic Laboratory Bulletin, No. 124, Washington, pp. 43–87.

Neal, Josephine B. Collected studies from the Bureau of Laboratories, 1921. City of New York, Dr. W. H. Park, Director. Vol. IX, pp. 13–52.

Worster, Drought and Kennedy. Cerebrospinal Fever. The Edinburgh Medical Series, 1919, London, A. and C. Black, 514 pp.

BIBLIOGRAPHY

Aaser, P. Ueber Meningokokkenserum. Beiträge z. Klin. d. Infektionskr., 1914, ii, p. 247; abstr. in Zeit. f. Immunitätsforsch., Ref., ix, No. 6, 255.

Conner, L. A., and Stillman, R. G. A pneumographic study of respiratory irregularities in meningitis. Arch. Int. Med., 1912, ix, 203.

Costa, S., and Troisier, J. Epididymite tardive, consecutive a une méningite cérébro-spinale provoqués par un paraméningocoque ayant les caractères fermentatifs du gonocoque. Bull. Soc. méd. d. hôp., 1917, xli, Nos. 33 and 34, pp. 1227-1229.

Councilman, W. T., Mallory, F. B., and Wright, J. H. Epidemic cerebrospinal meningitis and its relation to other forms of meningitis; a report of the State Board of Health of Mass., Boston, 1898. Wright & Potter Printing Co., State Printers, 178 pages.

Crowe, H. Warren. Some aspects of the cerebrospinal fever problem. Lancet, 1915, clxxxix, No. 4812, 1127-1133.

Crowe, S. J. On the excretion of hexamethylenamin (urotropin) in the cerebrospinal fluid and its therapeutic value in meningitis. Bull. Johns Hopkins Hosp., 1909, xx, No. 217, pp. 102-105.

Dandy, Walter E., and Blackfan, Kenneth D. Internal hydrocephalus. Am. Jour. Dis. Child., 1914, viii, No. 6, pp. 406-483.

——— Internal Hydrocephalus (Second paper). *Ibid.*, 1917, xiv, No. 6, 424-444.

Darre, H., and Dumas, J. Nouvelle espèce de paraméningocoque. Pluralité des paraméningocoques. Compt. rend. Soc. de biol., 1914, lxxvii, 106.

Davis, David J. Studies in meningococcus infection. Jour. Infect. Dis., 1907, iv, 558-581.

Dopter, Ch. Action antiendotoxique du sérum antiméningococcique préparé par inoculation intraveineuse de cultures vivantes de méningocoques. Compt. rend. Soc. de biol., 1909, lxvi, 772-774.

——— (2) Précipitines méningococciques et co-précipitines. *Ibid.*, 1055-1057.

——— (3) Étude de quelques germes isolés du rhino-pharynx, voisins du méningocoque (paraméningocoques). *Ibid.*, 1909, lxvii, No. 2, pp. 74-76.

——— Remarks on paper by Darré and Dumas. *Ibid.*, 1914, lxxvii, No. 2, 108-109.

——— Observations on serotherapy for cerebrospinal meningitis. Med. Bull. Am. Red Cross Soc., Paris, 1918, i, No. 5, pp. 338-340.

——— (2) La méningite cérébro-spinale dans la zone des armées pendant la guerre. Bull. de l'Acad. de méd., 1918, lxxix, No. 8, 169-171.

——— (3) Diagnostic et traitement de la méningite cérébro-spinale. Libraire J.-B. Baillière et Fils, Paris, 1918. 96 pages.

Dopter and Pauron. La saturation des agglutinines et des precipitines appliquée à la différenciation du méningocoque et des paraméningocoques. Compt. rend. Soc. de biol., 1914, lxxvii, No. 3, 157-159.

——— (2) Différenciation des paraméningocoques entre eux par la saturation des agglutinines. *Ibid.*, 231-233.

——— (3) La "saturation des bacteriolysines" appliquée a la différenciation du méningocoque et des paraméningocoques. *Ibid.*, 292-294.

Dubois, Phoebe L., and Neal, Josephine B. Streptococcus meningitis, with report of a cured case. Arch. Pediat., 1915, xxxii, No. 1.

——— Summary of 7 years of clinical and laboratory experience with meningitis in New York City. *Ibid.*, 1917, xxxiv, 561-590.

Dufour, R. Du liquide céphalo-rachidien hemorrhagique dans un cas d'insolation. Compt. rend. Soc. de biol., 1909, lxvi, 209-210.

Dunn, Charles Hunter. Cerebrospinal meningitis; its etiology, diagnosis, prognosis and treatment. Am. Jour. Dis. Child., 1911, i, No. 2, 95-112.

——— Pediatrics: the hygienic and medical treatment of children. The Southworth Co., Troy, N. Y., 2 vols., 1917.

Duval, Chas. Septicemia with acute purulent pericarditis and hypopyon-iritis caused by meningococcus. Jour. Med. Research, 1908, xix, n. s. 14, 259.

Eastwood, Arthur. Bacteriological aspects of the meningococcus carrier problem. Jour. Hyg., 1916, xv, No. 3, pp. 405-445.

——— Report on bacteriological aspects of the meningococcus carrier problem. Rep. to Local Govern. Board, on Pub. Health and Med. Subjects, 1917. Further reports on cerebrospinal fever, n. s. No. 114, pp. 1-51.

Ellis, A. W. M. Classification of meningococci based on group agglutination obtained with monovalent immune rabbit serums. Brit. Med. Jour., 1915, ii, No. 2868, p. 881.

Elser, W. J. A contribution to the study of epidemic cerebrospinal meningitis. Jour. Med. Research, 1905, ix, No. 1, pp. 89-107.

Elser, Wm. J., and Huntoon, Frank M. Studies on meningitis. Jour. Med. Research, 1909, xx, n. s. xv, No. 4 (114), pp. 369-541.

Embleton, Dennis, and Peters, E. A. Cerebrospinal fever and the sphenoidal sinus. Jour. Roy. Army Med. Corps, 1915, xxiv, 468-470.

Fairley, N. Hamilton, and Stewart, C. A. Cerebrospinal fever. Commonwealth of Australia, Quarantine Service, Service Publication No. 9, 1916, Government Printer, Melbourne, Australia. 188 pages.

Felton, L. D., Hussey, P. G., and Bayne-Jones, S. The reaction of the cerebrospinal fluid. Arch. Int. Med., 1917, xix, No. 6, pp. 1085-1096.

Fildes, P., Baker, S. L., and Adshead, G. P. I. A report upon the several outbreaks of cerebrospinal fever in the Navy at Portsmouth, 1916-1917, pp. 5-87. II. The treatment of cerebrospinal meningitis by antimeningococcus serum at the Royal Naval Hospital, Haslar, 1915-16-17, pp. 89-154. Nat. Health Ins., Med. Research Comm., London, H. M. Stat. Office, 1918.

Fitzgerald, J. G. Mixed infection (meningococcus and pneumococcus) meningitis. Jour. Am. Med. Assn., 1918, lxxi, No. 12, pp. 969-970.

Flack, Martin. Report on cerebrospinal fever in the London district. Dec., 1915-July, 1916. Nat. Health Ins. Med. Research Comm., London, 1917, Spec. Rep. Series, No. 3, pp. 31-64.

Flatten, Hans. Die übertragbare Genickstarre im Regierungsbezirk Oppeln, im Jahre 1905, und ihre Bekämpfung. Klin. Jahrb., 1906, xv, 211-298.

Flexner, Simon. Contributions to the biology of Diplococcus intracellularis. Jour. Exper. Med., 1907, ix, No. 2, pp. 105-141.

——— (2) Experimental cerebrospinal meningitis in monkeys. *Ibid.*, 142-167.

(3) Concerning a serum therapy for experimental infection with Diplococcus intracellularis. *Ibid.*, 168-185.

Results of the serum treatment in 1300 cases of epidemic meningitis. *Ibid.*, 1913, xvii, No. 5, pp. 553-576.

Flexner and Amoss. Chemical *vs.* serum treatment of epidemic meningitis. *Ibid.*, 1916, xxiii, No. 6, pp. 683-701.

Flexner and Barker. A contribution to our knowledge of epidemic cerebrospinal meningitis. Am. Jour. Med. Sc., 1894, cvii, 155-172, 259-276.

Flexner and Jobling. Serum treatment of epidemic cerebrospinal meningitis. Jour. Exper. Med., 1908, x, 141.

——— (2) An analysis of 400 cases treated with the antimeningococcus serum. *Ibid.*, 690.

Florand, A. Un cas d'orchiépedidymite à paraméningocoques, complication d'une méningite cérébrospinale. Arch. de méd. et pharm. mil., 1917, lxvii, No. 1, pp. 109-112.

Foster, Michael. Discussion on meningitis. Med. Bull., Am. Red Cross Soc., Paris, 1918, i, No. 5, pp. 346-350.

Foster, Michael, and Gaskell, J. F. Cerebrospinal fever. 1916. Cambridge Univ. Press. 222 pages. C. F. Clay, Fetter Lane, London.

Frost, W. H. Epidemic cerebrospinal meningitis. Public Health Reports, 1912, xxvii, No. 4, pp. 97-121. Revised and reprinted, 1919.

GASKELL, J. F. Report from the cerebrospinal fever laboratory, Cambridge, July, 1915. Jour. Roy. Army Med. Corps, 1915, xxv, 286-318.

GLOVER, J. A. The cerebrospinal fever epidemic of 1917 at X Depot. Jour. Roy. Army Med. Corps, 1918, xxx, No. 1; Jour. Hyg., Vol. xvii, Nos. 2 and 3, pp. 350-365.

——— (2) "Spacing out" in the prevention of military epidemics of cerebrospinal fever. Brit. Med. Jour., 1918, ii, 509.

GOEPPERT, F. Ueber Genickstarre. Ergebn. d. inn. Med. u. Kinderh., 1909, iv, 165-254.

GORDON, MERWIN H. Identification of the meningococcus. Jour. Roy. Army Med. Corps, 1915, xxiv, 455-458.

——— The definition of the meningococcus. Nat. Health Ins., Med. Research Comm., London, 1917, Spec. Rep. Series, No. 3, pp. 10-30.

——— (2) Bacteriological measures adopted for dealing with the military outbreak in February, 1915, and improvement effected as the result of research. *Ibid.*, 1-9.

——— Discussion on meningitis. Med. Bull., Am. Red Cross Soc., Paris, 1918, i, No. 5, 342-346.

——— (2) Identification of the meningococcus. Jour. Roy. Army Med. Corps, 1918, xxx, No. 1, 1; Jour. Hyg., xvii, Nos. 2 and 3, pp. 290-315.

——— (3) Production of meningococcus anti-endotoxin. Brit. Med. Jour., 1918, ii, No. 3013, p. 335.

GORDON, M. H., AND FLACK, MARTIN. Investigation concerning the disinfection of meningococcal carriers. *Ibid.*, Nov. 18, 1916, No. 2916, pp. 673-678.

GORDON, M. H., HINE, T. G. M., AND FLACK, MARTIN. Experimental study of the cultural requirements of the meningococcus. *Ibid.*, 678-684.

GORDON, M. H., AND MURRAY, E. G. Identification of the meningococcus. Jour. Roy. Army Med. Corps, 1915, xxv, 411-423.

GRIFFITH, FRED. Identification of meningococcus in nasopharynx, with special reference to serological reaction. Jour. Hyg., 1916, xv, No. 3, pp. 446-463.

——— Second report on identification of the meningococcus in the nasopharynx, with special reference to serological reactions. Rep. to Local Govern. Board on Pub. Health and Med. Subjects. Further reps. on cerebrospinal fever. 1917, n. s. No. 114, pp. 52-110.

GWYN, N. B. A case of general infection by the Diplococcus intracellularis of Weichselbaum. Bull. Johns Hopkins Hosp., 1899, x, 112.

HALL, I. WALKER, AND PETERS, B. A. I. Changes in the agglutinability, fermentation reactions and absorptive capacities of the meningococcus during the acute attack. Jour. Roy. Army Med. Corps, 1916, xxvi, 399-421.

HANDA, H., AND NANJO, M. On epidemic meningitis in the 37th Infantry Regiment in 1912. Jour. Military Surg., Tokio, 1913, No. 43. Reviewed in Centralbl. f. Bakteriol., Ref., lxi, 82-83.

HEIMAN, HENRY, AND FELDSTEIN, SAMUEL. Meningococcus meningitis. 1913. J. B. Lippincott Co., Philadelphia and London, 313 pages.

HEMENWAY, JOSEPHINE. Constant presence of tubercle bacilli in the cerebrospinal fluid of tuberculous meningitis. Am. Jour. Dis. Child., 1911, i, No. 1, pp. 37-41.

HERFORD. Bakteriologische und epidemiologische Beobachtungen bei einer Genickstarre-epidemic in Altona. Klin. Jahrb., 1908, xix, 265-284.

HERRICK, W. W. The epidemic of meningitis at Camp Jackson. Jour. Am. Med. Assn., 1918, lxx, No. 4, p. 227.

——— (2) Intravenous serum treatment of epidemic cerebrospinal meningitis. Arch. Int. Med., 1918, xxi, No. 4, pp. 541-563.

——— (3) Early diagnosis and intravenous serum treatment of epidemic cerebrospinal meningitis. Jour. Am. Med. Assn., 1918, lxxi, No. 8, pp. 612-617.

HERROLD, R. D. The distribution of meningococci in the upper respiratory tract of carriers. *Ibid.*, 1918, lxx, No. 2, pp. 82-83.

Hine, T. G. M. Report on the supply department of the central cerebrospinal fever laboratory for the period Feb. 19, 1915, to Aug. 18, 1916. Nat. Health Ins., Med. Research Comm., London, 1917, Spec. Rep. Series No. 3, 91-98.

——— (2) On the rapid preparation of high titre agglutination serum for the meningococcus. *Ibid.*, 99-105.

Hirsch, August. Die meningitis cerebro-spinalis epidemica. Verlag. von August Hirschwald, Berlin, 1866.

——— Handbuch der historisch-geographischen Pathologie. Berlin, 1886, 2nd Ed., Vol. III.

Hollecton, H. D. Cerebrospinal fever in the Royal Navy from August 1, 1916, to July 31, 1917. Lancet, Jan. 19, 1918, i, 87-92.

Holt, L. Emmett. Observations on 300 cases of acute meningitis in infants and young children. Am. Jour. Dis. Child., 1911, i, No. 1, pp. 26-36.

Horder, Thomas J. Cerebrospinal fever. Henry Frowde, London, 1915.

Hurwitz, S. H., and Trauter, C. L. On the reaction of the cerebrospinal fluid. Arch. Int. Med., 1916, xvii, No. 6, pp. 828-839.

Jacobitz. Über Genickstarre. München. med. Wchnschr., 1905, lii, 2178.

Jobling, J. W. Standardization of the antimeningitic serum. Jour. Exper. Med., 1909, xi, No. 4, pp. 614-621.

Jochmann, G. Versuche zur Serodiagnostik und Serotherapie der epidemischen Genickstarre. Deutsch. med. Wchnschr., 1906, xxxii, No. 20, pp. 788-793.

Johnston, Meredith R. A study of normal and pathologic cerebrospinal fluids in children. Am. Jour. Dis. Child., 1916, xii, No. 2, pp. 112-129.

King, W. W. Early diagnosis of cerebrospinal meningitis by the examination of stained blood-films. Jour. Am. Med. Assn., 1918, lxxi, No. 25, pp. 2048-2050.

Kolle, W., and Wassermann, A. Untersuchungen über Meningokokken. Klin. Jahrb., 1906, xv, No. 2, p. 507.

——— (2) Versuche zur Gewinnung und Wertbestimmung einer Meningokokkenserums. Deutsch. med. Wchnschr., 1906, xxxii, No. 16, pp. 609-612.

Kolmer, John A., Toyama, Ikuzo, and Matsunami, Toitsu. The influence of active normal serum (complement) upon meningococci: (1) The opsonic activity of fresh normal serum alone and in combination with antimeningitic serum for meningococcus. (2) The bactericidal and protective value of fresh normal serum alone and in combination with antimeningitic serum and complement. Jour. Immunol., 1918, iii, No. 3, pp. 157-200.

Koplik, Henry. Epidemic cerebrospinal meningitis. In Osler and McCrae's Modern medicine. 1913, 2d Ed., i, 594-619. Philadelphia and New York.

——— Discussion of Dr. Wilcox's paper on MacEwen's sign. Tr. Am. Pediat. Soc., 1915, xxvii, 276.

Meningitis in the new-born and in infants under three months of age. Arch. of Pediat., 1916, xxxiii, 481-500.

Kraus and Bacher. Ueber Meningokokkenserum. Ztschr. f. Immunitätsforsch, Orig., 1909, iii, No. 1, pp. 9-33.

Krumbein and Diehl. 'Neue Untersuchungen zur Wertbestimmung des Meningokokkenserum. Arb. a. d. Inst. z. Erforsch. d. Infektionskrankh. in Bern, 1908, Heft 2, p. 1 (Jena).

Krumbhaar, E. B., and Cloud, J. H. Acute meningococcic endocarditis and septicemia. Jour. Am. Med. Assn., 1918, lxxi, No. 26, pp. 2144-2146.

Kutscher, K. H. Uebertragbare Genickstarre. In W. Kolle and A. von Wassermann's Handbuch der pathogenen Mikroörganismen. 1912, 2d Ed., Vol. IV, pp. 589-654.

Lancelin, R. Troie cas d'epididymite d'origine méningococcique. Bull. Soc. méd. d. hôp., 1917, xli, 1052.

Landry, A. A., and Hamley, W. H. Epidemic cerebrospinal meningitis at Camp Beauregard, La. Amer. Jour. Med. Sc., 1919, clvii, No. 2, pp. 210-219.

LATHAM, JOS. R. Epididymitis as a complication of meningitis. A study of 24 cases. Jour. Am. Med. Assn., 1919, lxxii, No. 3, pp. 175-177.

LAVINDER, C. H., FREEMAN, A. W., AND FROST, W. H. U. S. Public Health Service Bull., 1918, No. 91, pp. 66, 86, 87, 97.

LEAKE, J. P., BOLTEN, JOS., AND SMITH, H. F. U. S. Public Health Service, Public Health Reports, 1917, xxxii, No. 48, p. 1999.

LEISHMANN, SIR WM. Discussion on meningitis before Research Society of American Red Cross. Med. Bull., Paris, 1918, i, No. 5, pp. 350-352.

LIEBERMEISTER, G. Ueber Meningokokensepsis. München. med. Wchnschr., 1908, lv, 1978.

VON LINGELSHEIM, W. Die bakteriologischen Arbeiten der Königl. Hygienischen Station zu Beuthen in O. Schl. während der Genickstarre Epidemic im Winter 1904-5. Klin. Jahrb., 1906, xv, No. 2, pp. 373-488.

LOW, R. BRUCE. The prevalence and distribution of cerebrospinal fever throughout the world during recent years. Rep. to Local Govern. Board on Public Health and Med. Subjects. Reps. on cerebrospinal fever, 1916, n. s. No. 110, pp. 115-183.

MACKARELL, W. WRIGHT. Malignant endocarditis as a complication of epidemic cerebrospinal fever. Jour. Roy. Army Med. Corps, 1915, xxv, 353-356.

MACKENZIE, IVY, AND MARTIN, W. B. M. Serum therapy in cerebrospinal fever. Jour. Path. and Bacteriol., 1908, xii, 434-435, 539-548.

MACLAGAN, P. W., AND COOKE, W. E. Fulminating cerebrospinal fever: prognosis and treatment. Jour. Roy. Army Med. Corps, 1917, xxix, No. 2, pp. 228-232.

MARCOVICH, A. Meningokokken im kreisenden Blute. Wien. klin. Wchnschr., 1906, xix, 1312.

MARIE, PIERRE LOUIS. Deux cas de septicémie prolongée à type pseudo-palustre avec épisode méningée tardif dûs à des germes voisins du méningocoque. Guerison par le serum polyvalent antiméningococcique. Bull. Soc. méd. d. hôp., 1917, xli, 259-273.

MARTINI AND ROHDE. Ein Fall von Meningokokken-Septikämie. Berl. klin. Wchnschr., 1905, xlii, 997.

MATHERS, GEORGE. Mixed infection with the pneumococcus in epidemic meningitis. Jour. Am. Med. Assn., 1917, lxix, 1778.

MATHERS, G., AND HERROLD, R. D. Meningococcus carriers and bacteriology of epidemic meningitis. Jour. Infec. Dis., 1918, xxii, 523-533.

MAXCY, KENNETH F. Observations on the presence of the meningococcus in the blood. *Ibid.*, 1918, xxiii, No. 5, pp. 470-474.

McCOY, G. W., AND LEAKE, J. P. Official control of antipneumococcus and antimeningococcus serums. Public Health Reports, 1918, xxxiii, No. 32, pp. 1313-1316.

McCOY, G. W., WAYSON, N. E., AND CORBITT, H. B. The potency of antimeningococcus serum. Jour. Am. Med. Assn., 1918, lxxi, No. 4, pp. 246-248.

MEDICAL RESEARCH COMMITTEE. (National Health Insurance.) Report of the Special Advisory Committee upon bacteriological studies of cerebrospinal fever during the epidemic of 1915. (F. W. Andrewes, Wm. Bulloch, R. T. Hewlett.) London, 1916. Printed under the authority of His Maj. Stationery Office by Sir Joseph Causton and Stone, Ltd.

MESTREZAT, W., AND ANGLADA, J. Reaction méningée dans un cas d'urémie convulsive et comateux. Compt. rend. Soc. de biol., 1909, lxvi, 638-640.

MESTREZAT, W., AND GAUJOUX, E. Analyses du liquide céphalo-rachidien dans la méningite cérébro-spinale à méningocoques. *Ibid.*, 1909, lxvii, 364-366.

MILLER, D. J. MILTON. A case of meningococcus meningitis in the new-born, with interesting and unusual features. Arch. Pediat., 1917, xxxiii, 824. 826.

MINK, O. J. Points in the epidemiology of meningitis. Jour. Am. Med. Assn., 1918, lxx, No. 8, pp. 563-564.

MONGOUR, CH., AND BRANDEIS. Liquide céphalo-rachidien clair à la periode terminale d'une méningite cérébro-spinale à méningocoques et un mois après le début des accidents. Compt. rend. Soc. de biol., 1909, lxvii, 557-558.

Mongour, Ch., and Roche. Méningite cérébro-spinale. Reaction de Wassermann negative avec le liquide céphalo-rachidien, positive après injection intrarachidienne de sérum antiméningococcique. Compt. rend. Soc. de biol., 1909, lxvi, 1039-1040.

Neal, Josephine B. Treatment of cases of epidemic meningitis, illustrating the importance of frequent repetition of the injection. Jour. Am. Med. Assn., March 18, 1916, lxvi, 862-864.

——— The treatment of epidemic meningitis. Monthly Bull., Dept. of Health, City of N. Y., Sept., 1918.

Netter, Arnold. Efficacité du chlorure de calcium comme moyen préventif des eruptions après injections sous-cutanées de sérum. Effêts moins satisfaisants dans les injections intra-arachnoidiennes. Compt. rend. Soc. de biol., 1909, lxvii, 186-188.

——— Diversité des méningocoques. Predominance de deux types. Importance de leur distinction. Bull. Soc. méd. d. hôp., 1917, xli, 882-886.

——— (2) Differenciation des méningocoques par l'agglutination. *Ibid.*, Nos. 33-34, pp. 1231-1236.

——— Discussions on meningitis. Med. Bull., Am. Red Cross Soc., Paris, 1918, i, No. 5, pp. 340-342.

Netter, Arnold, and Debré, Robert. Liquide céphalo-rachidien limpide au cours des méningites cérébro-spinales. (Première note: Liquide clair pendant les vingt-quatre premières heures de la maladie.) Comp. rend. Soc. de biol., 1909, lxvi, 866-868.

——— (2) Les eruptions seriques après injections intrarachidiennes de sérum antiméningococcique. *Ibid.*, 976-979.

——— (3) Liquides céphalo-rachidiens limpides à une periode avancée de la maladie. *Ibid.*, 1009-1011.

——— (4) Eruption sériques après injections intrarachidiennes. Constatation du sérum de cheval dans le sang après les injections dans le canal rachidien. *Ibid.*, 1909, lxvii, 100-101.

——— (5) Liquide céphalo-rachidien limpide au cours des méningites cérébrospinale. (3° note) Liquides normaux dépourvus de microbes dans les formes atténuées et abortives. Pouvoir agglutinant du sang vis-à-vis du méningocoque. *Ibid.*, 252-254.

——— Le méningite cérébro-spinale. Masson et Cie, Paris, 1911. 292 pages.

Netter, Arnold, and Salanier, Marien. The presence of meningococci in the purpuric elements of meningococcal infection. Brit. Jour. Child. Dis., 1917, xiv, 101-104, 104-106.

Neufeld, F. Weitere Untersuchungen über die Wertbestimmung des Genickstarreserums. Arb. a. d. K. Gesundh., 1910, xxxiv, No. 3, pp. 266-285.

Newsholme, Arthur. Preliminary memorandum. Reports on cerebrospinal fever. Rep. Local Govern. Board on Public Health and Med. Subjects, London, 1916, n. s. No. 110, pp. 3-5.

——— Further repts. on cerebrospinal fever. *Ibid.*, 1917, n. s. No. 114, pp. i-xiii.

Nichols, J. B. The numerical proportions of the sexes at birth. Am. Anthropol. Assn. Memoirs, Lancaster, Pa., 1907, i, pt. 4, pp. 249-300.

Nicolle, Debain E., and Jouan, C. Sur les méningocoques et les sérum antiméningococciques. Bull. Soc. méd. d. hôp., 1917, xli, Nos. 25-26, pp. 878-881.

——— Étude sur les méningocoques et les sérums antiméningococciques. Ann. de l'Inst. Pasteur, 1918, xxxii, No. 4, pp. 150-169.

Nowland, R. E. Notes on the treatment of 35 cases of cerebrospinal meningitis. Med. Jour. of Australia, 1916, ii (3d year), No. 24, pp. 489-492.

Onaka, M. Ueber Meningokokkenserums. Ztschr. f. Hyg., 1910, lxvi, 348-356.

Ong, Harry A. The serum treatment of epidemic cerebrospinal meningitis. Report of cases. Arch. Pediat., Oct., 1913, xxx, 781.

Ponder, Constant. A bacteriological investigation of organisms resembling the meningococcus found by examination of the nasopharynx of persons who had not been in contact with cases of cerebrospinal fever. Rep. to Local Govern. Board on Public Health and Med. Subjects, 1917, n. s., No. 114, pp. 159-214.

Pringle, Sir John. Observations on the diseases of the army in camp and garrison. Hospital or jail fever. London and Ed., 1753. Printed for A. Millar, pp. 243-301.

Pybus, F. C. Case of fulminating meningococcus septicemia. Lancet, 1917, i, 803.

Raffaeli, G. Sulla presenza del meningococci nel sangue. Gaz. d. Osp., 1917, xxxviii, 665.

Redden, Wm. R. Meningococcus carriers: preliminary report from the First Naval District. Boston Med. and Surg. Jour., 1918, clxxviii, No. 19, pp. 623-631.

Reece, R. J. Notes on the prevalence of cerebrospinal fever among the civil population of England and Wales during the last four months of the year 1914 and the first six months of the year 1915, together with a short account of the appearance of the disease and of its distribution among troops in the British Isles during the same period, and of the military administrative measures adopted to deal with prevalence of the disease. J. Roy. Army Med. Corps, 1915, xxiv, 555-568.

——— Anthrax simulating cerebrospinal fever. Lancet, 1917, cxcii, No. 11, p. 406-410.

Regan, Joseph C. A clinical consideration of MacEwen's sign. Am. Jour. Dis. Child., 1918, xvi, No. 1, 13-23.

——— Anatomic points determining the direction of the needle and the proper route for lumbar puncture in children and adults. Am. Jour. Med. Sc., 1919, clviii, No. 1, p. 83-99.

Richardson, Dennett L. The hospital control of the infectious diseases of infancy and childhood. (Before Pediatric Section, New York Acad. Med.) Arch. Pediat., 1916, xxxiii, 687-691.

Robb, Gardiner. Discussion on cerebrospinal meningitis. Brit. Med. Jour., 1908, ii, 1341.

Robey, W. H., Saylor, H. L., Meleney, H. E., Ray, H., and Landmann, S. A. Clinical and epidemiological studies on epidemic meningitis. Jour. Inf. Dis., 1918, xxiii, No. 4, pp. 317-336.

Robinson, G. C. Bacteriological findings in 15 cases of epidemic meningitis, with special reference to isolation of meningococci from the conjunctiva and the circulating blood. Bull. Ayer Clin. Lab. Pennsylvania Hosp., Philadelphia, 1906, No. 3, pp. 27-43.

Rolleston, H. D. Discussion on cerebrospinal meningitis. Practitioner, London, 1915, xcvi, No. 1, pp. 12-15.

Rosanoff, Aaron J. Certain residuals of epidemic cerebrospinal meningitis observed in the Army. Jour. Amer. Med. Assn., 1918, lxxi, No. 18, pp. 1476.

Ruppel, W. G. Ueber den Diplococcus intracellularis meningitidis und seinen Beziehungen zu dem Gonococcus. Deutsch. med. Wchnschr., 1906, xxxii, No. 34, pp. 1336-1368.

Russell, F. F. Discussion on meningitis. Jour. Am. Med. Assn., 1918, lxxi, No. 8, pp. 617, 644.

Sainton, P. Meningococcemia. Paris méd., 1918, viii, No. 31, pp. 86-91.

Salabert and Louis. Cytologie du liquide céphalo-rachidien dans la méningite cérébro-spinale. Rôle phagocytaire des cellules endothéliales. Compt. rend. Soc. de biol., 1909, lxvi, 770-772.

Salomon, H. Ueber Meningokokkenseptikämie. Berl. klin. Wchnschr., 1902, xxxix, 1045.

Sandison, A. Cerebrospinal meningitis. Med. Jour. of Australia, 1916, i (3d yr.), No. 11, pp. 220-222.

Schloss, Oscar M., and Schroeder, Louis C. Nature and quantitative determination of the reducing substance in normal and pathologic cerebrospinal fluid. Am. Jour. Dis. Child., 1916, xi, No. 1, pp. 1-11.

Scott, W. M. Study of meningococci occurring in spinal fluid and similar organisms in nasopharynx. Jour. Hyg., 1916, xv, No. 3, pp. 464-484.

——— A further study of the serological reactions of meningococci from the spinal fluid and the nasopharynx, with special reference to their classification and to the occurrence of the latter among normal persons. Rep. to Local Govern. Board on Pub. Health and Med. Subj., 1917, n. s. No. 114, pp. 111-158.

Sedgwick, Julius P. Discussion on meningitis in the new-born. Tr. Am. Pediat. Soc., 1915, xxvii, 255.

Sharpe, C. T. Meningococcic meningitis with unusual hemorrhagic manifestations and demonstration of the diplococcus in the skin. Arch. Pediat., 1916, xxxiii, 641-648.

——— Edema of the brain in the infectious diseases. Jour. Am. Med. Assn., 1919, lxxii, No. 3, pp. 159-162.

Shearer, Creswell. The toxic action of dilute pure NaCl solutions on the meningococcus. Lancet, 1916, cxci, 902-904.

Shennan, Theo., and Ritchie, W. T. A bacteriological investigation of epidemic cerebrospinal meningitis. Jour. Path. and Bacteriol., 1908, xii, 456-486.

Short, J. T. Epidemiology of cerebrospinal fever at Naval Training Station, Great Lakes, Ill. U. S. Naval Med. Bull., 1918, xii, No. 4, pp. 627-639.

Sophian, Abraham. Epidemic cerebrospinal meningitis. 1913, St. Louis, C. V. Mosby Co. 272 pages.

——— Posterior basic (walled off) meningitis. Report of a case with recovery. Am. Jour. Dis. Child., 1917, xiii, No. 6, p. 514.

Stade, C. Hyg. Rundschau, 1908, xviii, No. 9, pp. 519-527.

Stetten, De Witt, and Roberts, Dudley. Ventricular drainage by puncture of the corpus callosum in an obstructive hydrocephalus due to epidemic cerebrospinal meningitis. Jour. Am. Med. Assn., 1919, lxxii, No. 4, pp. 244-247.

Stewart, C. Alwyn. Cerebrospinal fever. Med. Jour. Australia, 1917, i (4th year), No. 16, pp. 333-336.

Symmers, Douglas. Status lymphaticus. Am. Jour. Med. Sci., 1918, clvi, No. 1, p. 57.

Symmers, W. St. Clair, and Wilson, W. James. Some points bearing on the bacteriology of cerebrospinal meningitis. Jour. Hyg., 1909, ix, 9-16.

Taylor, Frank E. Antibody content of cerebrospinal fluid in meningococcal infections. Lancet, March 17, 1917, 418.

Thomsen, O., and Wulff, F. Meningococcus infection and meningitis. Hosp.-Tid., Copenhagen, 1917, lx, No. 49, p. 1192. Abst., Jour. Am. Med. Assn., lxx, No. 7, p. 498.

Treadgold, C. H. Cerebrospinal meningitis in the Salisbury Plain area during the early part of 1915; a laboratory study. Jour. Roy. Army Med. Corps, 1915, xxiv, 221-230.

Tulloch, W. J. On the differentiation by means of the absorption of agglutinin test of the types of meningococci obtained from the cerebrospinal fluid of cases during the current outbreak of cerebrospinal fever. *Ibid.*, 1917, xxix, No. 1, pp. 66-90.

——— A study of the mechanism of the agglutination and absorption of agglutinin reaction, with an examination of the efficiency of these tests for identifying specimens of the meningococcus isolated from 354 cases of cerebrospinal fever. *Ibid.*, 1918, xxx, No. 2, pp. 115-146.

——— (2) Report on the examination of carriers isolated from 10,000 men in the garrison of X., April, May, June, 1916. Nat. Health Ins. Med. Research Comm., London, 1917, Spec. Rep. Series, No. 3, pp. 70-76.

Vaughn, Victor C., and Pratt, Geo. T. The communicable diseases in the National Guard and National Army of the U. S. during 6 months from Sept. 29, 1917, to March 29, 1918. Military Surg., 1918, xliii, No. 3, 251-265.

Vincent, H. Sur le précipito-diagnostic de la méningite cérébro-spinale. Compt. rend. Soc. de biol., 1909, lxvi, 759.

Vines, H. W. C. Some observations on the agglutination reaction of the meningococcus among carriers. Jour. Path. and Bacteriol., 1918, xxii, No. 1, pp. 56-73.

Walker, E. W. Ainley. A contribution to the study of meningococci. Jour. Hyg., 1918, xvii, No. 4, pp. 380-408.

Warfield, L. M., and Walker, J. K. Acute ulcerative endocarditis caused by the meningococcus. Bull. Ayer Clin. Lab. Pennsylvania Hosp., Philadelphia, 1903, No. 1, pp. 81-88.

Weed, Cushing, and Wegeforth. Studies on the cerebrospinal fluid. Jour. Med. Research, 1914, xxxi, No. 1, pp. 1-176.

Weed, Lewis H., Wegeforth, Paul, Ayer, Jas. B., and Felton, Lloyd D. The production of meningitis by release of cerebrospinal fluid during an experimental septicemia. A preliminary note. Jour. Am. Med. Assn., 1919, lxii, No. 3, pp. 190-193.

Weichselbaum, A. Ueber die literarischen Schicksale des Diplococcus intracellularis meningitidis und seine ätiologische Bedeutung. Centralbl. f. Bakteriol., 1903, Abt. I, xxxiii, No. 7, pp. 510-531.

Weiss-Eder, Stephanie. Ueber Komplikationen und Serumtherapie bei Meningitis cerebrospinalis epidemica. Med. Klinik., 1908, iv, No. 35, pp. 1337-1342.

Welsh, D. A., and Brown, Wolfe S. The intensive specific treatment of epidemic cerebrospinal meningitis. Med. Jour. of Australia, 1916, ii, 113-117.

Westenhöffer, M. Pathologische Anatomie und Infektionsweg bei der Genickstarre. Berl. klin. Wchnschr., 1905, xlii, 737-743.

——— Ueber den gegenwärtigen Stand unserer Kenntnis von der übertragbaren Genickstarre. *Ibid.*, 1906, xliii, 1267-1271, 1313-1316.

(2) Pathologisch-anatomische Ergebnisse der oberschlesischen Genickstarreepidemie von 1905. Klin. Jahrb., 1906, xv, pp. 657-728.

Ueber die praktische Bedeutung der Rachenerkrankung bei der Genickstarre. Berl. klin. Wchnschr., 1907, xliv, No. 38, pp. 1213-1216.

Wilcox, Herbert B. MacEwen's Sign. Tr. Am. Pediat. Soc., 1915, xxvii, 268-276.

Wilson, W. James. On heterologous agglutinins, more particularly those present in the blood serum of cerebrospinal fever and typhus fever cases. Jour. Hyg., 1909, ix, No. 3, pp. 316-340.

Wilson, Purce, and Darling. Certain points observed with regard to cerebrospinal fever in the Belfast Military District during 1915 and up to Nov., 1916. Brit. Med. Jour., December 30, 1916, 900-904.

Wollstein, Martha. Biological relationships of Diplococcus intracellularis and Gonococcus. Jour. Exper. Med., 1909, ix, No. 5, p. 588.

——— Influenzal meningitis and its experimental production. Am. Jour. Dis. Child., 1911, i, No. 1, pp. 42-58.

——— Parameningococcus and its antiserum. Jour. Exper. Med., 1914, xx, No. 3, pp. 201-217.

Worcester-Drought, C. Observations on treatment of cerebrospinal fever. Brit. Med. Jour., Nov. 18, 1916, 689-690.

Worcester-Drought, C., and Kennedy, A. M. Cerebrospinal fever. Mode of invasion by the meningococcus. Lancet, 1917, ii, 711-714.

Zaloziecki, Alex. Zur Frage der "Permeabilität der Meningen" inbesondere Immunstoffen gegenüber. Deutsch. Ztschr. f. Nervenh., 1913, xlvi, 195-211.

Zingher, Abraham. The value of ventricular puncture for the early diagnosis and serum treatment of posterior basilar meningitis. Am. Jour. Med. Sc., 1919, clvii, No. 1, pp. 58-67.

CHAPTER VII

DIPHTHERIA

By Samuel Sidney Woody, M.D.

Definition, p. 131—Etiology, p. 131—Predisposing causes, p. 131—Exciting cause: the organism, p. 132—Symptomatology, p. 135—Clinical history, p. 135—Second attacks, p. 137—Diagnosis, p. 137—Differential diagnosis, p. 139—Complications and sequelæ, p. 144—Association with other diseases, p. 148—Clinical varieties, p. 149—Treatment, p. 153—Prophylaxis, p. 153—Active immunization by means of toxin-antitoxin, p. 153—General management, p. 158—Medicinal treatment, p. 159—Local treatment, p. 160—Surgical treatment, p. 160—Intubation, p. 161—Extubation, p. 161—Tracheotomy, p. 162—Treatment of complications, p. 163—Management of convalescence, p. 164—Prognosis, p. 165—Pathology, p. 165—Historical summary, p. 169.

Definition.—Diphtheria is an acute, febrile, contagious infection, caused by a specific bacillus, characterized by the presence of a false fibrinous membrane deposited on the focus of infection, and accompanied by specific, toxic, systemic manifestations, affecting principally the heart and the nervous system. The site of infection is, in the vast majority of cases, the membrane of the throat; sometimes the nose and the larynx are involved, and more rarely the conjunctiva and cutaneous surfaces that are deprived of epithelium.

Etiology.—PREDISPOSING CAUSES.—Diphtheria is distributed practically all over the world and is endemic at all times, although it seems to show a preference for *northern climates* and for the cold, damp, winter months. *Sudden changes in temperature* from warm to cold seem to affect the incidence and the mortality of the disease. This fact is probably due to the catarrhal conditions of the nose and throat which result from a sudden fall in temperature, and which favor the lodgment and the growth of the diphtheria bacillus in these parts. *Soil conditions* are sometimes believed to affect the incidence of the disease, since epidemics of diphtheria have been known to originate in the vicinity of stables and in places where refuse vegetable matter has collected and decomposed, thus, through drainage, seriously contaminating the soil.

Diphtheria is decidedly a disease of *childhood*, without any noteworthy distinction as to *sex*. The susceptible period is that between the second and twelfth years, the most critical time being between the second and fifth years. Infants enjoy the same comparative immunity as they do from other acute infections. Adults, though less susceptible than children, may contract the disease at any time, although it is rarely seen in old age.

The general susceptibility to diphtheria is, on the whole, not nearly so marked as is the case with scarlet fever or measles. Observations show that in the vast majority of individuals who have been exposed to the disease, although the diphtheria bacillus is present, the infection never develops. Any personal predisposition that exists seems to be attributable, primarily, to the *condition of the mucous membranes,* particularly those of the nose and throat. Children who have adenoids, large or diseased tonsils and chronic inflammation of the nasopharynx, or deformities of the nasal septum, are much more likely than others to contract the disease. This is sometimes termed an increased superficial predisposition, and may also result from any other abnormalities of the pharyngeal or nasal regions.

The *presence of another acute infection,* particularly when of the anginose variety, such as scarlet fever and measles, is an important factor in the etiology of diphtheria. (The association of the two diseases is discussed on p. 251 of this volume.) In such instances the throat conditions present a most favorable opportunity for the diphtheria organism to become active.

The disease is in no way dependent upon *social conditions,* the rich and the poor being equally susceptible, except that, as in other infections, bad housing conditions, poor drainage, under-nourishment, etc., increase the disposition of the less-favored classes to disease in general. This applies also to *local racial conditions* and accounts for the apparently greater prevalence of the disease among the colored population in a given locality.

EXCITING CAUSE: THE ORGANISM.—Diphtheria is one of the few diseases the specific organism of which is known, and for which there is a specific treatment. To Klebs belongs the distinction of having first described the diphtheria organism (1883), while Löffler (1884) was the first to obtain it in pure culture. Later (1887), he succeeded in producing the disease in guinea pigs (rats and mice appeared to be insusceptible); it is known to be also transmissible to other animals—cats, dogs, horses and goats. Shortly after Löfler's demonstration, Roux and Yersin (1888) were able to show that the symptoms of diphtheria were due largely to a soluble toxin which is not part of the organism, but is secreted by it. Acting upon this suggestion, Ferran, and later Fraenkel and Brieger (1890), attempted active immunization against diphtheria with the toxin. At the same time von Behring made his discovery of the antitoxin, and after prolonged research in collaboration with Wernicke he was able to demonstrate by animal experiments the prophylactic and therapeutic value of the antitoxin. The first clinical tests on the human subject were made (1891) in von Bergmann's clinic at Heidelberg. The method at once gained adherents and, through the impetus thus acquired, it has become probably the most significant and valuable contribution to preventive and therapeutic medicine.

Morphology.—The Klebs-Löffler bacillus is aërobic, being most satisfactorily cultivated in an alkaline medium (Löffer's blood serum) at a temperature of about 98° F. (36.6° C.). It is generally described as a

Gram-positive, rod-shaped, slender organism with rounded ends, varying in size from 1 to 6 microns in length and from 0.3 to 0.8 microns in diameter. It is easily stained with anilin dyes, the Löffler alkaline solution of methyl-blue being among the best and the one in which it appears smallest and most constant. Its appearance, however, is not altogether constant, polymorphism being one of the characteristics of the diphtheria organism. Westbrook, whose classification is the one generally accepted in this country, divides it into three morphological groups, each with subdivisions according to the size of the organism. The first group is the beaded or granular type (with deep staining granules) and is designated A, B, C, D; the second is barred or banded (having transverse bands), and is designated A_1, B_1, C_1, D_1; the third is a solid type taking an even stain, and is known as A_2, B_2, C_2, D_2. Westbrook, in his original grouping, recognized variations up to the letter G, but in the working laboratory the above subdivisions have proved sufficient.

At the laboratory of the Philadelphia Bureau of Health, cultures are pronounced positive only when they show: A or A_1, B or B_1, C or D. C_1, D_1, the shorter barred forms, and B_2, C_2 are considered avirulent, but cultures showing these and other atypical forms should not be pronounced negative until they have been re-incubated for another 24 hours; unless the field, after the second incubation, shows the above positive types (A or A_1, B or B_1, C or D) the culture can be considered negative.

The granular type is the one most commonly seen early in the disease, whether it be localized in the nose, the pharynx or the larynx. This type is apt to prove virulent even in prolonged culture cases, so that contacts showing it should be held under suspicion of being dangerous until proved otherwise. Later in the disease this type is supposed to be replaced by the barred or by the solid forms. This, however, is a matter of controversy. In the City Bacteriological Laboratory of Philadelphia the granular type has been found throughout the disease until the very end.

In a study of the cases at the Philadelphia Hospital for Contagious Diseases, made by Kolmer a few years ago, the barred type was distinctly rare; but at present, at the City Bacteriological Laboratory of Philadelphia, it is being met with continually in a small percentage of cases. Kolmer, who regards this type as avirulent, found it present in 20 per cent. of cultures taken from the healthy penis.

The solid type is the more serious form. The bacilli of this group are few in number and are replaced later by the granular type. It is generally supposed to be present only in the late stage of the disease, but some authorities believe that it is also present in the earlier cultures, but is overshadowed by the granular type; the Philadelphia city bacteriologists find the long B_2, C_2 type present in early cases and in young cultures.

It is when this type predominates that the advantage of animal inoculation is greatest. The longer bacilli show a greater tendency to retain their virulence than the shorter ones. Both, however, may be descendants of the so-called carrier bacillus rather than of the organism that produces the clinical evidence of the disease. The shorter, solid types are most frequently found in the nose when clinical manifestations of diphtheria are absent. In a majority of cases these bacilli are not pathogenic, although in a small percentage they are virulent, as proved by animal inoculation.

The long solid types are frequently found in otitis media, and in our experience they are always avirulent.

Cultivation.—In making the cultures it should be borne in mind that the *broth* used should be *neutral* or slightly alkaline, since the diphtheria bacillus produces acid very rapidly, especially with glucose, and a high acidity inhibits and finally kills the organism. The toxins are usually elaborated in 48 hours in animal experiments.

Attention is called at this point to the pseudo-diphtheria (Hoffmann) bacillus and *Bacillus xerosis,* which often enter into consideration in differential diagnosis and which are frequently seen in the conjunctival fluid. The differentiation is best made by acid production tests, the most satisfactory medium being Hiss's serum-water, colored with azolitmin and containing 1 per cent. respectively of the following sugars: glucose, saccharose, dextrin, lactose, maltose, galactose and mannite. The results are recorded after the cultures have been incubated for five days at 95° F. (35° C.); the presence of acid is shown by the blue turning to pink or red. Virulent diphtheria bacilli frequently produce acid with dextrose and dextrin in the order mentioned; the results with the other sugars are variable. Cultures which prove negative as far as the structure of the organism is concerned but produce acids with some of the sugars, notably glucose and dextrin, are to be regarded as non-virulent diphtheria bacilli, and a negative report should be given when they appear in cultures.

These sugar tests are most useful in studying cultures from the eye, and are the only means of differentiating the short solid type from the Hoffmann bacillus and the *Bacillus xerosis.* If the culture proves non-virulent for pigs, and produces no acid with any of the sugars, it is regarded as containing Hoffmann bacilli, while non-virulent types that produce acid with saccharose are regarded as cultures of *Bacillus xerosis.*

Distribution.—The diphtheria bacillus differs from other pathogenic organisms by the fact that it is widely distributed throughout the body. It is found not only on the surface of the affected mucous membrane, and in the superficial portions of the false membrane and its underlying tissues, but also, in the severe cases, in the heart-blood, the liver, spleen and kidneys.

The most important characteristic of the diphtheria toxin (its chemical composition has not yet been determined) is to stimulate the production of antibodies which, when injected into the human body in proper doses, create a certain degree of immunity and resistance to the disease.

Modes of Conveyance.—The *source of contagion* of diphtheria is preeminently the ***human subject,*** that is, the diphtheria patient, who emits infected droplets while talking or coughing. Tracheotomized croup cases are a most dangerous source for the spread of the disease, since such patients are apt to cough up shreds of membrane through the cannula.

There is little positive evidence that the *soil,* the *water* or the *milk supply* are factors in disseminating diphtheria, except that impurities in the water or the milk, or defective drainage, may be responsible for the lowered resistance of the mucous surfaces to disease.

The diphtheria bacillus is remarkably resistant to cold, retaining its virulence for several months during the winter, but its resistance is lowered by exposure to light and to moisture. It shows no particular resistance to disinfectants, but it is apt to retain its virus to a remarkable degree for many months if protected from light, and allowed to dry, for example, on a *particle of membrane,* or on *fomites,* such as toys, books, eating and cooking utensils, or, more especially, on *bed* and *body linens* that have come in contact with a diphtheria patient. According to some authorities the bacillus is also present in the *urine* of patients, and the nurse or attendant is apt to be infected in this way unless properly protected.

Danger of contagion persists into the period of convalescence and beyond it, even into the ninth week or longer. The observation that the diphtheria bacillus on the membrane of convalescents often retains its virulence for a more or less prolonged period after convalescence, together with the fact that healthy individuals in the vicinity of the diphtheria patient also harbor the specific organism, is supposed to account for certain mysterious epidemics of diphtheria through the medium of such direct and intermediary *carriers* of the organism.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The typical infection from the bacterial toxin is manifested by local and general phenomena.

For various reasons the incubation period of diphtheria cannot be definitely determined, but it is generally short, from two to four days, rarely exceeding seven days, depending on the virulence and the number of organisms present, and on the susceptibility of the individual. The maximum incubation period has lost its importance since the introduction of the custom of culturing the throats of all contacts as a routine measure.

The diphtheritic membrane is apt to develop in different parts of the body. Its clinical course depends upon the particular location in which it is deposited, the most common situation being the faucial region, which will serve as a basis for our description of the clinical history of the disease.

Mode of Onset.—The early symptoms are the languor, apathy and general loss of appetite and vigor that accompany an incipient cold. This may last a day or two before the child complains of *pain in the throat,* although sometimes, aside from the general malaise, sore throat is the only complaint. More rarely the invasion is sudden, accompanied by chills, high fever, 100° to 103° F. (37.8° to 39.4° C.), headache, nausea and vomiting, together with the throat symptoms; but the latter sometimes do not appear until the end of the first or the beginning of the second day. It is important to remember that the degree of fever is no criterion for the future course of the disease. It may be low at this stage in a severe and fatal case, or high in what proves to be a mild case. At this early stage the patient, on examination (the opportunity for which occurs more often in private than in hospital practice), will present a pallid countenance, rapid soft pulse (110-120), and a disagreeable odor from the mouth. The tongue is dry and moderately coated; the faucial mucosa is slightly reddened and shows increased mucous secretion. Sometimes one or even both tonsils will be the site of a small, grayish opal coating or of a grayish, cloudy patch. The membrane at this stage is only slightly adherent and can be easily and safely removed. It will be found (under the microscope) to consist of fibrin, epithelial cells, leukocytes, diphtheria bacilli and the usual buccal flora. If removed, the membrane rapidly reforms; when allowed to remain it becomes firm, consistent and more intimately adherent to the underlying tissues, with a tendency to spread to the surrounding structures—the anterior and posterior pillars of the fauces and the lateral margins of the uvula—the latter often being so entirely covered as to suggest a finger encased in a glove.

Within the next twenty-four hours the membrane assumes its characteristic grayish aspect, the intensity of color depending upon the other organisms present. When thin the membrane is translucent; it may also be a pale yellow or a dirty white or even dark, almost black, if there is bloody effusion. It is now tough, firmly adherent, and when removed leaves a raw, bleeding surface. Later on in the course of the disease, as the membrane begins to separate of its own accord, it can be removed without producing bleeding.

The subjective symptoms produced by the presence of the membrane on the throat are burning and difficulty in swallowing; the swelling of the tonsils makes the voice rough and thick, while the inflammation may, as early as the first day, cause enlargement of the glands, especially the maxillary, those at the angle of the jaws and the anterior cervical groups. This glandular involvement may appear as early as the first day. Sometimes it is slight and accompanied by very little tenderness; in the more advanced cases it may be severe, with the formation of "bull-neck"—a collar of matted and enlarged glands all around the neck. Suppuration is not likely to occur except in cases of mixed infection, where there may be sloughing of the infiltrated mass.

The toxic effect of the disease is also seen in the general symptoms which it causes. The *temperature* rises to 100-102° F. (37.8°-38.9° C.) in the moderate cases, and up to 104° F. (40° C.) in the more severe ones, falling by lysis in both. The severe cases are accompanied by the usual manifestations of hyperpyrexia, and in young children occasionally by convulsions. The fever, however, is greatly modified by serum therapy.

The *pulse* and *respiration* correspond to the temperature, but often the pulse in children is much more rapid than the fever warrants.

Pallor and apathy, prominent features of the disease, increase and indicate the effects of the toxin.

The *blood* shows moderate leukocytosis, the increase being in polymorphonuclear cells. Myelocytes are also present, especially in fatal cases. There is a marked reduction in the red blood-corpuscles, which may fall as low as two million or even five hundred thousand, with a corresponding diminution in the hemoglobin percentage to 10 or 30 per cent. Patients with the latter symptom recover much more slowly than those with the former.

Albuminuria is very common, so much so that it is considered a part of the symptom-complex of diphtheria. It may appear at any time from the third to the seventh day, in amounts varying from a slight trace to a considerable percentage, and may persist for several weeks. Acute nephritis with hyaline and epithelial casts is rare, although it may occur.

With the early administration of antitoxin in sufficient dosage, the progress of the disease is promptly arrested. The membrane begins to separate, falling off piecemeal and also disappearing by absorption, which begins at the margins and is completed in two or four days, according to the size of the membrane, sometimes leaving a delicate grayish infiltration which persists for a few days more. The mucosa, relieved of the membrane, appears markedly red. The fever begins to subside within 24 hours after the injection and reaches the normal on about the third day, when the patient begins to feel comparatively well. Sometimes mild as well as severe cases will give negative cultures almost immediately after the parts become normal in appearance. Others, even very mild ones, will continue to give positive cultures indefinitely for weeks or even for months. There is nothing in the local condition to account for the one or the other phenomenon.

Without serum therapy the course of the disease, in favorable cases, is protracted over from eight to fourteen days. The membrane adheres firmly, generally spreading over the entire throat and often involving the neighboring structures. The difficulty in swallowing is intense and agonizing. Prognosis is uncertain. Although recovery may take place, there is always the danger of laryngeal involvement with stenosis, as well as of the sudden development of heart symptoms leading to death; death may occur at the end of the second week from heart complications, nephritis or bronchopneumonia.

SECOND ATTACKS.—An attack of diphtheria does not confer the same immunity against the disease as results after other acute infections, such as small-pox, scarlet fever and measles. Relapses may take place during convalescence, or the disease may recur in three or four weeks or any time after recovery. As a rule, the relapse (occurring during or shortly after convalescence) is not so serious as the original attack, although death may occur during a relapse. Second attacks or even third attacks at remote periods after the first one are not at all uncommon and are dependent upon the individual disposition to the disease and the opportunity for infection.

Diagnosis.—There is perhaps no medical condition in which early

diagnosis entails a greater responsibility than in diphtheria or cases that suggest diphtheria. Inasmuch as we have at our disposal a prompt and effective means of controlling diphtheria in its early stages (within the first 24 to 36 hours), it is not too much to say that when confronted with a suspicious case the doctor, unless he is one hundred per cent. sure that it is not diphtheria, should at the first visit administer antitoxin in full dosage. This is essential for the salvation of the patient, for the protection of the public and for the reputation of medicine in general and of the individual physician in particular. In view of this it seems almost superfluous to discuss the diagnosis of diphtheria, more especially since the clinical picture and the bacteriological findings often fail to harmonize, and much valuable time is lost in arriving at a diagnosis. Therefore, treat and then diagnose, is the order of procedure to be observed in the presence of a sore throat or other symptoms which arouse the slightest suspicion of diphtheria, for the efficacy of serum treatment depends upon its early administration.

The clinical symptoms of diphtheria, as already enumerated, are sometimes so modified as to be misleading. In young children, for example, there is often little discomfort in the throat, and not until the glandular enlargement and the pharyngeal symptoms are marked will attention be called to the throat. Inspection of the throat, therefore, should be a part of the routine examination in all disorders of childhood.

In the diagnosis of diphtheria we can to some extent be guided by the age of the patient, the location and appearance of the lesions and the clinical manifestations of fever and albuminuria.

As regards age, it is well to remember that children do not often suffer from throat conditions such as tonsillitis, quinsy and other anginas with which diphtheria is likely to be confused, so that, provided scarlet fever and thrush can be excluded, any visible patching of the throat of a young child should be treated as diphtheria.

As to the location of the lesion, in diphtheria it generally affects the pillars of the fauces, the uvula or the soft palate. And, although Vincent's angina may often have to be considered, it is safe to act on the suspicion of diphtheria. Primary lesions of the buccal mucosa, while they may be due to thrush, should be considered as diphtheria until proven otherwise.

The true diphtheritic membrane is often described as pearly gray in appearance. But in reality the color is no index, since it is seen in every shade from a dead white, or a yellow, to even a deep black. While the adherence of the membrane and the raw surface that its removal often leaves may be taken as positive indication of diphtheria, the absence of these features cannot be relied upon as contra-indicating the disease. It must be remembered that the diphtheritic membrane soon begins to separate spontaneously, and the case may come under observation at the time when the membrane is more or less easily detached. And as to the bleeding surface it leaves, it has been proven that even in cases of true diphtheria the deposit has been removed without leaving such a surface.

With regard to the other clinical symptoms, it is well to remember that the combination of low fever or even subnormal temperature with a patched but not painful throat and albuminuria is apt to indicate diphtheria, since in other throat conditions the temperature is usually high, and the throat painful. It is especially the low temperature together with albuminuria that should arouse suspicion.

Differential Diagnosis.—Faucial diphtheria is likely to be confused with *tonsillitis, quinsy,* the *ulcerative sore throat of Vincent's angina,* with *syphilitic* and *tuberculous angina, thrush, herpes* and, finally, *scarlatinal angina.*

Acute tonsillitis differs from faucial diphtheria in that the pain in the throat is more severe, there is more generalized redness, the temperature is high, the face flushed, the pulse full and bounding and the tenderness of the enlarged cervical glands much more marked. In fact, there is a preponderance of general, constitutional symptoms, especially pain in the head, back and extremities, not noted in diphtheria. The exudate of tonsillitis may very closely resemble that of diphtheria in its early stage, in that it may spread over a portion of the tonsils or the posterior faucial pillar. There may also be a superficial slough which strongly suggests diphtheria, but the fact that the membrane is easily removed and when separated rarely leaves a bleeding surface is evidence in favor of tonsillitis. Very often, however, the differentiation is possible only after repeated bacterial examination.

The differentiation from *quinsy* should as a rule be easy, since suppuration of the tonsils in diphtheria is most unusual, and the tonsillar enlargement in quinsy gives the back of the throat a one-sided appearance, while the soft palate on the affected side is apt to protrude forward and downward. With these distinguishing signs diphtheria can generally be excluded, even though there be a small amount of exudate present. But often after a tonsillar abscess has been incised the resulting grayish wound may resemble a diphtheritic membrane. It differs from the latter by the fact that the membrane does not spread and that the tonsillar enlargement is peripheral only. In some instances confusion may be due to the thin film that settles on the tonsils when the abscess ruptures high up and at the back of the tonsils, and from which pus exudes at every attempt to swallow; sometimes the film assumes the character of a well-organized membrane. Inspection of the throat is difficult because the patient is unable to open the mouth, the latter symptom being an almost infallible indication of quinsy, and often in such circumstances a diagnosis of diphtheria will be made. Giving antitoxin in such a case can do no harm, but inspection (when possible) and the ease with which the membrane wipes off should solve the question. Quinsy can also often be recognized by a fluctuating mass, felt on palpating with the fingers. In some rare instances, however, true diphtheria is also accompanied by an excessive amount of peritonsillar inflammation and by other symptoms of quinsy which make differentiation difficult. This further emphasizes the importance of prompt administration of antitoxin in ample dosage.

Vincent's angina is usually unilateral and is characterized by a greenish gray membranous formation on an ulcerative base which, like the diphtheritic membrane, is not easily wiped off, while a strong fetid odor from the mouth may also suggest diphtheria. It differs from the latter in that the membrane is not influenced by antitoxin, persists for a longer time (about fourteen days), that local symptoms and fever are not marked, and finally in its bacteriology. Spirillæ and fusiform bacilli are present in such large numbers as to suggest pure cultures. It is important to remember, however, that spirillæ and fusiform organisms may often be associated with diphtheria bacilli. They are sometimes so numerous as compared with the latter, if studied without a culture, as to lead to a false diagnosis of Vincent's angina. Therefore, where there is the least doubt a search for diphtheria bacilli should be included in the bacteriological examination of smears from a suspected case of Vincent's angina.

Syphilitic ulceration in the throat also frequently suggests diphtheria, especially since the removal of the slough may cause slight hemorrhage and the temperature may remain normal. But the absence of constitutional symptoms, the location of the lesions well forward in the throat, and usually also on the hard palate, the character of the slough, which is apt to be depressed with the edges of ulceration well defined, together with the history of the case, the possible presence of syphilitic lesions elsewhere, the failure of diphtheritic serum therapy and the results of specific treatment, will generally point to the true nature of the disease.

In *tuberculous ulcerating sore throat,* the chronicity and the presence of tuberculous lesions elsewhere should render differentiation easy.

In differentiating faucial diphtheria from *thrush* it should be noted that the patches of thrush are milky white in color, and occur in almost any situation, even on the tongue and lips. But they are not surrounded by inflammation and are easily wiped off, while the underlying tissue is normal. Under the microscope the patches reveal mycelia and spores.

In *herpes* the tonsils are often the site of numerous vesicles which on rupturing leave grayish sores. But unlike diphtheria, herpes is nearly always accompanied by violent headache and also by the presence of lesions on other parts of the buccal mucosa, especially the lips. Epidemics of herpes and diphtheria are often concurrent, so that the presence of lesions on the lips should not rule out diphtheria, and the proper precautions should be instituted.

The chief source of confusion of faucial diphtheria is with *scarlatinal angina.* At first thought, especially to the inexperienced, this may seem incredible, since the typical case in each disorder presents distinct and widely divergent symptoms. But hospital experience teaches that confusion often occurs, and with disastrous results. Differentiation is of the utmost importance and, indeed, presents one of the most vital problems in fever hospital management.

The confusion occurs, not only in those aberrant cases of scarlatina in which the exanthem is so slight as to escape detection, and where desquamation has not yet set in, but also in the more regular case where the throat symptoms during the first two or three days may be highly suggestive of diphtheria. The uncertainty is furthermore enhanced by the very frequent association of the two diseases.

One of the most reliable symptoms in those cases which are examined on the fourth to the sixth day of the disease is the presence of the "strawberry tongue" and its tendency to desquamation; this can usually be taken to indicate scarlatina. In other words, in borderline cases a pale, thinly-coated tongue, showing no tendency to desquamation after two or three days, is almost proof positive that the case is not scarlet fever. Another point of differentiation is the fact that in scarlatina the tonsils and the uvula are much redder than in diphtheria, the infiltration often extends to the hard palate, while the exudate which covers the tonsils in the form of small white specks consists of pultaceous débris which is easily wiped off and contains neither fibrin nor diphtheritic bacilli. The presence of the scarlatinal exanthem will, of course, clinch the diagnosis. The study of the palate, also, is often of much help in diagnosis. In scarlet fever the palate is quite consistently reddened and shows distinct elevations or punctæ. This is rarely seen in diphtheria, so that in doubtful cases a pale, smooth palate is strong evidence, in fact almost positive proof of diphtheria.

In the septic cases of scarlet fever with severe throat symptoms, the patient is flushed and restless, in marked contrast to the pallor and apathy that characterize diphtheria.

As to other early symptoms, neither vomiting, rhinorrhea nor glandular enlargement are of much aid. Vomiting, although quite a constant initial feature of scarlatina, may also be present in diphtheria; rhinorrhea is a feature of both diseases, and the glandular enlargement in severely septic diphtheria may be as pronounced as in scarlatina. On the other hand, albuminuria is not apt to appear as early in scarlatina as in diphtheria, and may thus serve in differential diagnosis. In some instances the differentiation cannot be made until the third week of the disease, when the typical pinhole desquamation, or symptoms of nephritis or of arthritis, will settle the doubt, if it has not already been cleared up by bacteriological examination.

The differentiation of laryngeal diphtheria from non-diphtheritic laryngeal obstruction or *croup* sometimes presents considerable difficulty. If during the course of faucial or nasal diphtheria symptoms of stenosis set in, the diagnosis is plain. But in cases of primary laryngeal diphtheria the differentiation is not easy. It is therefore a safe rule to consider symptoms of croup in a young child as suspicious, and to institute serum therapy at once without waiting for bacterial confirmation, more especially so since we know that reliance can be placed only upon positive and not upon negative evidence, and that in primary laryngeal diphtheria negative cultures mean less than in other forms and are therefore misleading. In some instances, after a careful examination the suspicion of diphtheria will fall away and it will be realized that the obstruction is due to some non-diphtheritic condition, such as laryngospasm, acute simple laryngitis, laryngismus stridulus, edema of the glottis, retropharyngeal abscess and influenza. In these the voice remains unchanged and respirations between attacks normal, whereas in laryngeal diphtheria, hoarseness and loss of voice are practically the rule.

Acute simple laryngitis, which often sets in with hoarseness and a croupy cough, is not accompanied by persistent stridor and contraction of the soft parts; it yields readily to treatment, such as placing the child at the open window in order to give it plenty of air, and the application of heat (hot flannels, or cloths wrung out of hot water). The history of a tendency to attacks of "croup," especially at night, the absence of constitutional symptoms and of a known exposure to diphtheria should rule out the latter. But well-marked and persistent dyspnea should arouse suspicion and no time should be lost in applying serum therapy.

Special attention is directed to the importance of differentiating an attack of "croup" during the course of *measles.* Laryngitis, which often appears in measles before the eruption breaks out, may be associated with marked inflammation and swelling of the laryngeal membrane leading to symptoms of obstruction with stridor and contraction; often small ulcerations will be found on the epiglottis. While the appearance of Koplik's spots is a reliable sign of measles, and demands the isolation of the patient, any doubt as to the true nature of the trouble should be sufficient indication for giving antitoxin.

Very often the convulsive spasms of *laryngismus stridulus* suggest laryngeal diphtheria. But it can be distinguished by the more or less prolonged apnea followed by crowing gasps after the spasm relaxes and frequently also by strabismus and actual convulsions. Furthermore, it rarely attacks children over two years of age and is generally a manifestation of rickets. Any of these signs should rule out diphtheria.

The most serious affection which is likely to be confused with laryngeal diphtheria is acute *edema of the glottis* occurring in connection with inflammatory or suppurative processes localized in the larynx or its vicinity, such as erysipelas, which may extend from the pharyngeal mucosa to the larynx and induce sudden obstructive symptoms; or severe phlegmonous angina may lead to acute edema of the glottis. Examination of the throat and the larynx and study of the history of the case will generally indicate the correct diagnosis.

Retropharyngeal abscess may also often suggest laryngeal diphtheria. But the difference appears on inspection of the pharynx, which often shows a fluctuating mass that can be seen or be felt with the fingers; the characteristic voice also serves to differentiate the two conditions. Furthermore, the onset is prolonged, extending over several days or a week; the patient throws back the head for the better admission of air; there is considerable difficulty in swallowing and the swelling of the neck is much more marked than in diphtheria. The voice is characteristic, best described as a harsh, guttural pharyngonasal sound, which once heard is never forgotten. The entire condition also shows evidence of a prolonged wasting illness.

During the severe epidemic of *influenza* in the fall of 1918, many cases were sent into the Philadelphia Hospital for Contagious Diseases with a diagnosis of laryngeal diphtheria, but which proved to be influenza with laryngeal symptoms so marked as to require intubation. The differentiation in favor of influenza rests upon the more pronounced constitutional symptoms, especially the prostration, which is much greater than in primary laryngeal diphtheria, also upon the greater tendency to develop pneumonia, the frequent and violent coughing resulting in autoextubation, of which there seemed to be a perfect epidemic in our recent experience, and finally upon the failure to respond to serum treatment as evidenced by the necessity of re-inserting the tubes in those patients who survived; for this together with the danger of pulmonary involvement renders the prognosis of these cases very unfavorable.

Other conditions that produce symptoms of laryngeal obstruction are the *urticaria* resulting from serum sickness, *papilloma of the larynx, acute swelling of the faucial tonsils* and more rarely *bronchial glandular tuberculosis*. A careful examination together with the history of the case should make the distinction clear in such instances.

Hyperplasia of the *thymus* is variously reported as simulating diphtheritic laryngeal obstruction. The chronic condition of the illness, the absence of hoarseness, except as the attacks recur, and *x*-ray evidence will point to the true cause of the trouble.

Differential diagnosis in many instances, as we have seen, can be made only after bacteriological examination. In urgent cases this can often be promptly obtained by the study of smears of the false membrane stained with methylene blue or carbol-fuchsin. If the case is diphtheria the specimen will show, in addition to fibrinous threads and the usual buccal flora, a few bacilli strongly suggesting the Klebs-Löffler organism. But the absence of the latter cannot be taken as reliable evidence that the disease is not diphtheria, so that cultural tests will have to be the deciding factor.

To obtain the material for a culture, a swab is firmly rubbed along the edges or under the membrane, care being taken not to touch the teeth or the tongue. The swab is then rubbed on the culture medium—Löffler's blood-serum—and incubated for twelve or eighteen hours at body temperature. In positive cases the culture will then be found to consist of streptococci, the usual buccal bacteria and colonies of diphtheria bacilli. The latter, after being collected on a platinum wire, are placed on a slide and stained with methylene blue (Löffler) for five minutes.

The protoplasm of the bacillus will take a blue stain and the granules a reddish-purple. The presence of the long or short organisms with beaded ends, with the above method of staining, may be taken as positive evidence of diphtheria. This reaction, especially in young cultures, is sufficient for the general practitioner; sometimes the differentiation between the Hoffmann bacillus and the rare form of diphtheria bacillus

The precocious type should be taken to predicate a more severe course of the diphtheria; it is often accompanied by cardiac symptoms and by the graver forms of paralysis.

The first signs of paralysis of the soft palate are a nasal twang to the voice and difficulty in swallowing, fluids being returned through the nose owing to incomplete closure of the nasopharynx. Inspection will show a lax condition of the pharynx and the uvula during phonation, and there may also be diminished sensibility of the palatine mucosa. Isolated palatal paralysis, as a rule, persists for two or three weeks, rarely beyond that time. The first sign of regression is improvement in the act of swallowing, followed later by resumption of the natural voice. Palatal paralysis is associated with paralysis of one or more muscles in about sixty per cent. of diphtheria cases; it is most often associated with that of the ciliary muscles.

Ciliary paralysis is next in frequency to the palatal affection. The patient usually complains of difficulty in accommodation; although when he starts to read the letters appear plain, they soon become blurred. This loss of accommodation is a comparatively early manifestation. It may and usually does appear during the third week of the disease, but may not set in until the seventh or eighth week; it rarely persists longer than five, the average being about three weeks. In young children, unable to read, this complication may often be missed. The phenomenon is occasionally accompanied by abductor paresis manifested by strabismus; less often it is associated with ptosis, and in rare instances with optic neuritis.

The *extremities* are involved in postdiphtheritic paralysis almost as often as the muscles of accommodation, and in about one-third of all cases the paralysis is limited to these regions. The lower members are usually the first to be affected, the symptoms often beginning with a creeping sensation and weakness in the legs, ataxic gait, and diminished or abolished patellar reflexes. There is often some disturbance of station, anesthesia and hyperesthesia, especially in the distal portions of the member. Sometimes the process is arrested at this stage of "acute ataxia," and normal conditions return in from four to six weeks. In more severe cases the ataxic symptoms are followed by paresis and degenerative paralysis of individual muscles (peroneus, etc.), the patient being unable to support the body. There is also flaccid paralysis with partial degenerative phenomena and associated involvement of the upper members as well as of the trunk and the nape of the neck. Even in the most pronounced cases recovery is the rule, especially after massive doses of antitoxin. But convalescence is often prolonged over two or three months, or more, and in some rare instances, especially after paralysis of the ulnaris, contractions may be permanent owing to atrophy of the interossei.

The most distressing and most fatal type of postdiphtheritic paralysis is that of the *respiratory muscles,* the intercostals, especially of the diaphragm. In isolated paralysis of the thoracics the diaphragm remains almost immobile during respiration, the act being carried on by the intercostals and other extraordinary muscles. Paralysis of the diaphragm is manifested by the absence of abdominal arching during inspiration, while if there is also a paresis of the abdominal muscles, expiration becomes increasingly difficult. Often there is an associated paralysis of the thorax which increases the distress and is frequently accompanied by dyspnea and paralysis of the larynx, necessitating tracheotomy. Death ensues either from respiratory paralysis or from aspiration pneumonia. Jochman observed this distressing generalized paralysis in 3.8 per cent. of 130 cases of postdiphtheritic pareses.

Paralysis of the *pharyngeal muscles* may also take place without generalized paralysis. It can be recognized by loss of voice, with a peculiar, high-pitched, rattling cough, a tendency to splutter while eating, and inability to swallow and to clear the throat. Food may pass into the larynx, producing complete sudden obstruction, or pneumonia may result from particles of food entering the lungs. Ker reports a case in which pulmonary tuberculosis developed after this type of "food pneumonia." The condition is serious because of the danger of the patient's choking to death. In severe diphtheria this type of paralysis may occur early and in conjunction with palatal paresis. But it usually takes place during the fifth to the seventh week of the illness and generally disappears in about ten days.

In addition to these—the more frequent and important postdiphtheritic paralytic manifestations—paralysis of almost any nerve, either isolated or in association with other nerves, may result from the effects of the diphtheria toxin. Fortunately, these pareses are rarely simultaneous but follow each other, the one appearing as the other improves. The prognosis is generally favorable, recovery being the rule.

A much dreaded and often fatal complication of diphtheria, which is especially liable to occur in the laryngeal cases, is *bronchopneumonia.* While it is mostly due to some other septic infection, particularly streptococcic, it may sometimes be purely diphtheritic in character. The symptoms are persistently high temperature, rapid respirations and more or less coughing. Fine crepitations may sometimes be made out, but more generally the physical signs are obscured owing to intubation or tracheotomy. In spite of the relief to the laryngeal obstruction afforded by the latter, the condition may spread, leading to death in two or three days. In the favorable cases, however, temperature and respiration subside gradually, reaching the normal in from ten days to three weeks.

It may also happen that the ear becomes infected by way of the eustachian tube, resulting in *otitis media.* The discharge, at first clear, soon becomes purulent, and may also be hemorrhagic. It generally subsides completely, and is very rarely so severe or extensive as to lead to mastoiditis; some authorities claim that it never occurs, but we have observed it in two cases in an experience of eleven years covering very nearly 21,500 cases.

The toxic effects of the disease are also seen in the emaciation of the patient, increasing almost to cachexia, and in the *nephritis* which sometimes appears as a complication of severe cases of diphtheria. Albuminuria, as we have seen, is commonly regarded as one of the symptoms of the disease, but in some instances, not necessarily only the severe cases, there is a true acute parenchymatous nephritis with excretion of large amounts of albumin (8 to 10 per cent.), casts and leukocytes. As a rule, however, severe malignant diphtheria is accompanied by constant albuminuria of 2 to 3 per cent. The urinary output is reduced, but not so much as in scarlatina, specific gravity is increased and urobilinuria is not uncommon. The urine is rarely blood-stained. Diphtheritic albuminuria in the favorable cases (those that do not succumb to heart or other complications) usually subsides in two weeks, and in the lighter cases in two or three days; it very rarely develops into chronic nephritis.

Association with Other Diseases.—Diphtheria is liable to be associated with one or more of any of the other acute infections, the most frequent combination being *scarlatina.* It may set in early in the scarlet fever, but in reality this is rather unusual. The pseudo-membrane of early scarlatinal angina is often so much like true diphtheria that, judged by the membrane alone, differentiation is almost impossible and can be made only after repeated cultures. It is this type which furnishes a large percentage of so-called, but not actual, mixed infections. The fact that a positive culture is occasionally obtained from these cases does not necessarily indicate true diphtheria, since it may represent a diphtheria carrier who happens to have developed scarlet fever. At the same time, it is best to give these patients the benefit of any doubt that may exist and to administer antitoxin at once. This is especially advisable in fever hospitals, inasmuch as it at once wards off the danger of diphtheria, at least during the acute stage of scarlet fever, and thus gives the patient a better chance of combating the scarlatina, which is not in any way influenced by the antitoxin.

It is from the third to the sixth week of the scarlet fever that the patients show the greatest susceptibility to diphtheritic infection. This cross-infection is more liable to occur in hospital than in private practice, since it may happen that a mild case of diphtheria will go undetected and thus become the source of infection for other scarlatinal cases. The course of a diphtheritic infection developing in these cases differs in no way from primary diphtheria, except that the prognosis may be unfavorably affected owing to the weakened condition of the patient. At the same time, when the cross-infection does occur in a fever hospital the prognosis is more favorable than in private practice because of the constant vigilance that prevails in a well-conducted hospital, which permits of prompt recognition as well as prompt treatment with antitoxin. On the other hand, scarlet fever developing on diphtheria may present an unfavorable outlook, inasmuch as the already damaged condition of the mucous membranes, especially of the throat, is apt to conduce to the severer manifestations of scarlatinal angina.

Measles also seem to show a particular predisposition to diphtheritic infection, the catarrhal condition presenting a focus of minor resistance.

In the majority of cases the diphtheria accompanying measles is of the laryngeal type. The croup may be preceded or accompanied by nasal diphtheria. Loss of voice, dyspnea and contraction of the soft parts of the chest during the course of measles should at once arouse suspicion and call for *immediate serum treatment.* The prognosis of the combination is grave on account of the danger of bronchopneumonia.

The same danger is present when diphtheria develops during *whooping-cough.* When thus associated the onset of the diphtheria is apt to be insidious, the pharynx remaining clear, and the first signs of the added trouble being obstructed breathing or a catarrh in one or both nostrils with a profuse mucopurulent discharge, cultures of which reveal the diphtheria bacillus. The diphtheritic process, after persisting for some days, often spreads to the pharynx, resulting in an acutely serious condition; or faucial or laryngeal diphtheria may also develop without the primary nasal invasion.

Diphtheria sometimes develops during *typhoid fever* and is apt to be mistaken for laryngeal manifestations of the latter. Symptoms of laryngeal stenosis during typhoid fever should arouse suspicion and unless diphtheria can be absolutely ruled out, should be combated by the prompt use of antitoxin.

The association of *varicella* and diphtheria is not uncommon, but is of little import as affecting the diphtheria. *Acute anterior poliomyelitis* with diphtheria is a more serious combination. During the epidemic of the summer of 1916 the two diseases were often associated and proved fatal in a number of instances in the author's experience.

Clinical Varieties.—Variations may occur, from the *severely malignant type* of diphtheria which yields neither to serum therapy nor to cardiac stimulation and runs a fatal course in three or four days, to the *less malignant type,* which, with prompt administration of antitoxin, may result in recovery, but in which the postdiphtheritic manifestations delay convalescence and continually threaten life, and to the *benign catarrhal type* presenting merely a catarrhal or follicular angina, diagnosable mainly by bacteriological cultures.

In the *malignant type* the invasive symptoms may be insidious, and the throat unobtrusive, although examination on the first day will reveal the presence of the typical membrane; or the invasion may be sudden and stormy. The membrane rapidly develops on the tonsils, the uvula and the soft and hard palate, and may extend to the nose, from which visible particles often protrude or are emitted on blowing the nose; it may also settle around the anterior nares and on eroded surfaces around the corners of the mouth. Hemorrhagic tendency is a feature of the very severely malignant faucial diphtheria and occurs into the skin surfaces, especially those of the extremities, the trunk and the forehead.

The patient's appearance is marked by extreme pallor, apathy and stupor. He breathes through the mouth, emitting a characteristic fetid odor. The membrane spreads widely over the fauces and tonsils, and is of a dirty gray color with dark, hemorrhagic central areas.

The pulse is rapid, and extremely soft and irregular. There is often a tendency to vomit, a very bad prognostic sign. Death generally results from cardiac failure, and may be sudden, due to the strain of vomiting, or it may be slow, occurring as late as the second week, or later, accompanied by manifestations of severe toxemia, paralysis of the heart or of other muscles, or of a low form of bronchopneumonia. The fever in the more favorable cases may rise to 102° F. (38.9° C.), but it soon falls and remains around 100° F. (37.8° C.). The liver and the spleen are swollen, and kidney involvement is manifested by albumin and casts in the urine. On about the sixth day the membrane begins to separate and the temperature soon returns to normal. But the patient is listless, emaciated, pale and weak. The edema of the neck subsides and the swelling and tenderness of the glands disappear. The membrane may separate in a mass, although sometimes it fades away so gradually that it is difficult to determine just how long the process lasts.

Convalescence is slow and often protracted by postdiphtheritic manifestations, especially paralysis of the muscles of the soft palate or of the pharynx, and by cardiac arhythmia.

The *benign catarrhal type* of faucial diphtheria is diagnosable mainly by bacteriological cultures. It generally runs a rapid course; although the temperature may rise to 102.2° F. (39° C.), it nearly always subsides in two or three days. This type may, however, develop into laryngeal croup, so that it is imperative to give all cases of angina developing in a diphtheritic environment antitoxin treatment.

In addition to this mild variety of faucial diphtheria there is an aberrant type which results from secondary pyogenic infection and which may lead to severe parenchymatous tonsillitis in which the tonsils are covered with the false membrane and the mucosa of the soft palate and of the hard palate is red and edematous, interfering with respiration and with swallowing. The tonsillar swelling usually subsides and only rarely is there abscess-formation which, if it occurs, necessitates incision and drainage.

Extension of the diphtheritic membrane from the fauces to the nose occurs in about twenty per cent. of cases; but *nasal diphtheria* may also be a primary manifestation of the disease. Rolleston observed it in 1.5 per cent. of 3,000 cases of angina. This type is particularly dangerous and is more generally fatal than the faucial type. Because of the difficulty of its early recognition, treatment is apt to be delayed, unless the membrane happens to localize within the nostril and can be seen on examination. Otherwise there is nothing that would arouse suspicion that the rather severe nasal catarrh, with more or less marked constitutional symptoms, is due to the presence of the diphtheria bacillus on the nasal mucosa, until the advance of the disease leads to unusual prostration and the discharge from the nose assumes a serosanguineous character; often the discharge of a fragment of membrane is the first hint of the true nature of the disease. By this time the toxemia will already have had a chance to get in its destructive work. If, however, simple nasal diphtheria is recognized early and is promptly treated with antitoxin there is no reason why it should be any more dangerous than the simple faucial disease. With a history of exposure to diphtheritic infection, every discharging or dirty nose should be considered as a probable case of diphtheria and should have antitoxin treatment at once.

Sometimes infection is carried by way of the eustachian tube to the ear, which presents inflammatory symptoms and, at times, contraction of the ear-drum. The onset of *diphtheritic otitis* is usually insidious, not making its appearance until the faucial or pharyngeal diphtheria is on the wane. The symptoms are gradually increasing pain in the ear, often progressing quickly to perforation of the ear-drum, and the discharge of a seropurulent or sanguinopurulent secretion. The prognosis of diphtheritic otitis is generally favorable; it rarely develops into mastoiditis, and hardly ever leaves any trace of impaired hearing. Diphtheria may also attack the tongue and the mouth, but the condition is very unusual.

Laryngeal diphtheria or croup, like the nasal variety, is dangerous because of the difficulty of inspection and the consequent delay in serum treatment. The infection may be primary, or it may result from infection from faucial diphtheria. In the primary type the usual constitutional symptoms are often wanting, either because death may ensue from obstruction before the symptoms of toxic absorption have had a chance to appear, or because the larynx, compared to the pharynx, possesses a weaker power of absorbing toxins.

Laryngeal diphtheria is more apt to occur in very young children than in older ones, and in view of the narrowness of the infantile larynx and the tendency to convulsions, laryngeal croup is always a serious matter in a young child. As a rule, the first indication of the trouble is huskiness of the voice with a typical barking, ''brassy'' cough, soon succeeded by loss of voice, inspiratory stridor, recession of the soft parts of the chest, cyanosis, restlessness, and rapid, weak, irregular pulse.

Very often the condition is preceded by a cold in the head, of one or two days' standing, which differs very little from an ordinary rhinitis, except that the diphtheria bacillus will be found in the secretion; or the discharge may be seropurulent and the resulting excoriation around the nose may arouse suspicion of the nature of the secretion.

In older children and in adults extensive involvement of the larynx, the trachea and even the bronchi may occur unaccompanied by urgent symptoms; the patient may cough up membranous casts of these structures and recovery may take place without any operative interference; in the severe toxic cases the patient dies, not from the diphtheria, but from cardiac failure.

Laryngeal diphtheria is the type most likely to develop when diphtheria supervenes as a secondary manifestation of one of the other acute infections, especially measles and whooping cough, the combination being particularly serious on account of the tendency to bronchopulmonary involvement presented by the primary, as well as by the secondary—the laryngeal—diphtheritic infection.

Bronchopneumonia, in fact, represents one of the great dangers of diphtheria of the larynx, either through invasion of the diphtheritic organism or from secondary pyogenic infection. Very often the complication is the direct cause of death, and at autopsy in such a case the membrane will be found on the trachea, the bronchi and even on the bronchioles. During life the membrane may be coughed up, although this is not as usual now as formerly, before the introduction of antitoxin, and occurs only in advanced and neglected cases. Sometimes the separation of a larger piece of membrane in the trachea or larynx may cause suffocation, which can be relieved only by immediate tracheotomy.

In most cases tracheotomy, if performed between the second and the fourth day, and the prompt administration of antitoxin lead to a rapid regression of the distressing symptoms. The fever subsides in two or three days, the diphtheritic process is inhibited and particles of membrane are coughed up through the tube or cannula; generally the tube can be removed in two or three days.

In cases that do not come to treatment until the fifth or the sixth day, tracheotomy may relieve the local symptoms, but serum therapy instituted as late as that will scarcely modify the systemic effects of the toxemia, especially on the heart, so that the condition generally develops the severely malignant picture of diphtheria, ending in death.

Tracheal diphtheria is the type in which the exudate and the inflammation are below the glottis; the voice is then, of course, not affected and the cough will not be croupy. The symptoms of obstruction, however, may be just as marked as in laryngeal diphtheria. When the disease is limited to the larynx and the trachea there is little toxemia, and the symptoms are those of mechanical obstruction with possibly fatal suffocation as the ultimate result. Late heart-failure and paralysis are rare.

The temperature remains elevated, especially if the lungs are involved; but when the laryngeal and tracheal affection are associated with the faucial and nasal types of diphtheria, the temperature remains consistently normal unless there is pulmonary involvement. Adenitis is present only when the laryngeal infection is an extension from the throat and nose.

As already indicated, the diphtheritic membrane may develop anywhere on abraded mucous or skin surfaces. *Cutaneous diphtheria* is more common among children than among adults, and most frequently develops on the anal and genital regions, in the form of small ulcers which generally heal quickly, or in the form of a membrane with considerable edema of the surrounding parts. The membrane may develop on the conjunctiva, either directly or from infection from the faucial or nasal types of the disease. The eye symptoms in such cases vary according to the deep or superficial character of the affection. In the presence of diphtheria elsewhere, any eye symptoms should receive attention.

Wound diphtheria results from infection of a wounded surface either from scratching or from contagion from a case of diphtheria. Postdiphtheritic paralysis is not unusual in such cases, and it is interesting to note that the paralysis begins in the affected parts, as, for example, paralysis of the thumb when that member has been the site of infection. The fingers are often infected, especially in young diphtheritic patients who are apt to put the fingers into the mouth; often in this way faucial diphtheria develops from transference of the membrane that has developed primarily on the fingers; and the physician's fingers, while performing intubation, may be infected in this way through some slight wound. The result is usually a more or less painful bleb which bursts and results in a sore covered with specks of diphtheritic membrane.

Treatment.—A logical sequence of topics in the discussion of diphtheria would require treatment to precede diagnosis, for, as has been already indicated, *treat and then diagnose* is the one safe method when the physician is confronted with a throat which arouses the slightest suspicion as to its innocent nature. Conformity, however, demands that treatment be considered at this time.

PROPHYLAXIS.—Active immunization of all children is to-day receiving considerable attention. The advocates of this procedure are hopeful that its general application will bring about the same reduction in morbidity and mortality as obtains from vaccination against small-pox.

Active Immunization by Means of Toxin-antitoxin (T. A.).—This method was first suggested by Theobald Smith and put to a practical test by von Behring. In this country it has been brought to some degree of perfection, particularly by the investigations of Park and Zingher. These authors find that those individuals who give a negative Schick test (*see below*) after the age of two or three years are probably immune for life. For those who are not immune and for whom a longer immunization than that derived from the antitoxin is desired, they advise the use of **toxin-antitoxin**, which they claim provides lasting immunity in from 95 to 100 per cent. of susceptible individuals. This is shown by their observation that during subsequent exposure to diphtheria, children thus inoculated did not develop the disease, the immunity persisting for at least three years, the Schick test having again proved negative at that time. For the treatment of diphtheria contacts, T. A. is not as valuable as the antitoxin because in the majority of cases the immunity develops slowly; susceptible individuals should therefore be given both. For the protection of a community or the inmates of an institution for a number of years, T. A. is of the utmost value. For general prophylaxis it is given in doses of 85 to 90 per cent. of the L_+ dose of toxin to each unit of antitoxin, three injections of 1.0 c.c. each (of the T. A.) administered subcutaneously at intervals of one week. This is given to adults who give a positive Schick reaction and to children over eighteen months of age. The administration of the toxin-antitoxin thus early in life confers immunity at least for the period of the child's greatest susceptibility to diphtheria.

In the presence of what appears to be a case of diphtheria, the **isolation** of the patient is imperative under the same general measures as those described for the scarlet fever patient (pp. 255-259 of this volume). **Quarantine is not essential** since cultures of exposed persons are always taken, and if these are found to be negative and there are no symptoms of the disease, there is no necessity for detaining the subjects.

As regards the protection of contacts by antitoxin administration, we are not in favor of its indiscriminate use except in institutions harboring a number of children, or in general hospitals and fever hospitals where facilities for separating contacts are limited, and where, owing to reduced resistance, the susceptibility of contacts is probably increased. The protective value of antitoxin does not extend beyond three weeks; in fact, we have known it to last as short a time as eleven days. In view of this it must be borne in mind that the sensitized condition of the blood produced by the serum may result in anaphylaxis, which experience has shown may develop in those who have had an immunizing dose and later require a curative dose of the antitoxin owing to the subsequent development of diphtheria. Moreover, we have in the *Schick test* a method with which the susceptibility of those who have been exposed to the disease can with reasonable certainty be determined. This consists of intradermic injections, preferably into the arm, of a minute quantity of diphtheria toxin, a local reaction following if there is less than one-thirtieth of a unit of antitoxin per c.c. of blood, the amount considered sufficient to protect the bearer against diphtheria. If no reaction (except that from the puncture) follows within from twenty-four to thirty-six hours, the subject may be considered immune, that is, he possesses enough antitoxin to neutralize the injected serum. But in those who do not possess this antitoxin within themselves a positive reaction appears within from twenty-four to forty-eight hours in the form of a circumscribed area of redness about one-half centimeter in diameter, which persists for several days and gradually disappears, leaving a brownish pigmented spot with superficial scaling which may be visible for several months. A pseudo-reaction may sometimes take place, which can be recognized by its early appearance—within twelve hours—by its less well-defined area which is surrounded by a pinkish band, and by its disappearance within forty-eight hours. Sometimes for control an injection is made into the other arm, using 50 per cent. more of the serum than for the test arm, heated to 75° C. in order to destroy those qualities in the substance that are easily altered by heat.

It is interesting to note that in the negro the reaction is as clear-cut as in the white, the pigmentation being darker than the skin, and that the adult negro shows the same degree of immunity as the adult white. Lichenification occurs in all positive cases, regardless of the color of the skin, and promises to be of value in differentiating positive from negative reactions in those rare instances where an increase of pigmentation does not take place for one reason or another.

Separation and **isolation** of **contacts, culturing the throat,** and careful examination and inspection of the throat twice daily for the length of the incubation period, with the prompt administration of antitoxin at the slightest sign of trouble are, in the author's opinion, more advantageous than the indiscriminate use of antitoxin in the prophylactic treatment of contacts. But these measures are not always feasible, so that immunization becomes the more common measure, especially for those who give a positive Schick test.

The *immunizing dose* of antitoxin (any reliable preparation can be used) varies from 1,000 to 1,500 units, the larger dose being given to inmates of institutions or when exposure has been prolonged for five or six days. Infants from six to twelve months should have from 500 to 1,000 units, while for those less than six months the dosage may be reduced, down to 100 units for the newborn child, should it be found desirable to immunize such young children.

The injection is given intramuscularly and is ordinarily not followed by any reaction, except perhaps a very little local discomfort, a temporary rise of temperature and sometimes a transient urticarial, morbilliform or scarlatiniform rash.

Contacts, particularly young children, often appear to be suffering from a cold, which frequently proves to be diphtheria. Such a child should receive a curative dose and should be cultured and kept under observation.

The *curative dose* may be given subcutaneously, intramuscularly or intravenously. The *subcutaneous method* is rapidly falling into disuse owing to its slow absorption and to the greater and more prolonged discomfort attending the injections.

The *intramuscular* injection is simple, causing a minimum of discomfort; its action is, moreover, prompt and efficacious. The point of election is the anterior external surface of the thigh at the juncture of the upper and median thirds. The site, after being cleansed, is painted with **tincture of iodin**; the needle is then thrust well into the muscle, and unless the fluid is forced in with too great rapidity, little pain will be experienced. The wound should be closed with a small pledget of cotton and collodion.

In view of the fact that we are not in a position to determine with accuracy the virulence of a given attack, that is to say, the definite amount of toxemia with which we have to deal, the *dosage* will always, to a certain extent, be empirical, based largely upon experience. While in general the author is in favor of large doses, certain factors enter into consideration. These are the general condition of the patient, his age, the duration of the disease, the location and extent of the diphtheritic process on the day the antitoxin is administered, the patient's susceptibility and the virulence of the organism. We have no way of dealing with the last two, so that they need no further consideration.

The effect of the toxemia on the particular individual must be considered in estimating the amount to be given. Two patients who have been attacked at the same time under the same conditions may present widely differing degrees of toxemia, the one showing marked pallor, listlessness, prostration, together with pronounced glandular enlargement and albuminuria, while the other is not nearly so severely affected. The former will, of course, require a larger dose than the latter. But the amount should never be reduced below a certain working minimum to meet the probable requirements of a given case.

The age of the patient is of importance only in that infants under two years of age should have about half the amount necessary for older children and adults. The author rarely gives less than 5,000 units.

As to the duration of the disease, it is a matter of common experience that antitoxin given after the third day is much less efficacious and will require a larger dose than if given earlier. Therefore, in order to ensure the best results in arresting the disease and the avoidance of complications and sequelæ, the rule to be observed is *early administration and a sufficient dose at the first injection.* In general, it may be said that a larger dose than necessary does no harm, but an insufficient amount may result in the death of the patient. Usually one dose suffices to prevent the spread of the membrane; but if after from twelve to twenty-four hours the membrane appears to be extending and the general condition fails to improve, a *second* dose should be given.

Tonsillar cases in which the membrane is limited and the case is examined on the first day will require 10,000 units; if there is the least sign of dyspnea, 15,000 units must be given. A case examined on the second day of the disease should have at least from 15,000 to 20,000 units, and after that 20,000 units or more should be given.

In nasal cases where there is but slight moisture from the nares and diagnosis is made by cultures only, the dosage, if administered on the first day of the disease, should be 10,000 units or more, according to the time that has elapsed from the onset of the disease and the institution of serum therapy. However, in nasal cases where there is a distinct membrane with discharge and signs of toxemia, 20,000 units should be given as an initial dose on the first day of the disease, increasing to 30,000 or even to 50,000 units if seen as late as the third day.

The maximum total dosage that may be given to an individual during the course of the disease is limited only by the supply available for a single case rather than by any ill effects that may result from large doses. The author has known 300,000 units to be given (subcutaneously), resulting in recovery.

With the proper technic carried out under antiseptic precautions and the use of a reliable sterile serum, complications do not occur from the use of antitoxin. Abscess-formation at the site of injections is rare, especially if the intramuscular method is used, which avoids the marked and persistent soreness that follows the subcutaneous method.

Intravenous administration of antitoxin is particularly useful in the treatment of late, advanced cases. At the Philadelphia Hospital for Contagious Diseases it is also being used with excellent results in the moderately severe cases. It presents the great advantage of prompt action and of requiring a smaller dose than the other methods, and is therefore less expensive. Its prompt effect is readily explained when we consider that it is through the blood that the antitoxin is distributed to the place where it binds and neutralizes the toxins; it thus further prevents the toxin from passing out into the tissue cells. Park states that 5,000 units given intravenously are as effective as 20,000 given subcutaneously. Six hours after the injection the blood contains 20 units per c.c. of blood as against 2 units per c.c. of blood after subcutaneous administration of the serum. The membrane disappears more quickly; the patient feels well; the bacillus also disappears from the body sooner, and therefore the number of carriers is reduced; furthermore, fewer heart-failures and fewer cases of paralysis follow during the course of the disease.

The injection can be made in the vein of the arm, but when this is not easily done, as in young children, where, owing to the smallness of the vein, it will often be necessary to cut down to it, the external jugular forms a convenient site for the injection. There is generally less pain during and after the administration of antitoxin by this method than by the other routes. Antitoxin of high potency should be used, say 2,000 units per c.c. and diluted about one-half with physiological salt solution (the dilution being made in the laboratory), warmed to a little above body temperature and placed in an ordinary 5 c.c. or 10 c.c. glass syringe at the time of making the injection; for children a No. 22 and for adults a No. 19 gauge can be used. For ordinary cases, with membrane on both tonsils but not extending to the pillars, a dosage of 3,000 units should suffice and need not be repeated; for more extensive involvement a single dose of 5,000 should prove effective. In the more advanced and very desperate cases the author has given 10,000 and even 20,000 units with brilliant results. Sometimes in this type of patient it has been found advantageous to use both routes, that is, to reënforce the intravenous with the intramuscular injection of the serum.

If a high potency serum is used very little reaction results from its administration intravenously; any reaction that does occur is but transitory and not worthy of consideration in view of the advantages the method presents. The only disadvantage is the delicate technic, which requires experience and skill.

A *serum reaction* from the injection of antitoxin results in a varying percentage of cases. A few years ago the author observed it in 43.4 per cent. of 1,000 cases. The effect is manifested by an urticarial, morbilliform or scarlatiniform eruption accompanied by general malaise, fever, nausea, vomiting, violent itching, joint pains and sometimes edema. It is self-limited, requires no special treatment and is never serious.

Anaphylaxis, or serum sickness, on the other hand, is of moment in that it may lead to collapse and death. On the whole it is very rare, so that the urgent necessity of administering antitoxin entirely outweighs any danger that may be connected with its use. Indeed, in the face of a genuine Klebs-Löffler infection, we know of no contra-indication to the use of antitoxin. Some persons who have been sensitized by a previous dose of the serum, and others suffering from what is known as horse asthma exhibit a tendency to develop serum sickness. A skin test is useful for detecting such individuals. The test is made by scarifying the skin and applying a little serum. The appearance in from 2 to 15 minutes of an urticarial reaction indicates susceptibility. Such persons should be given serum treatment under special precautions and only after careful consideration as to which is the lesser of the two evils.

Often it becomes necessary to differentiate a serum rash from a true exanthem of infectious disease, such as measles, scarlatina, etc. The urticarial rash is, of course, easily recognized, especially with the knowledge that antitoxin has been administered, while the presence or absence of Koplik's spots and coryza will be sufficient indication of whether the eruption is due to measles or to the serum reaction. But with a scarlatiniform rash we cannot be so certain, and in view of the frequent association of the two diseases, it is best, especially in an institution, to treat all scarlatiniform rashes as scarlet fever and to isolate the patient from the diphtheria patients and, for obvious reasons, also from the scarlet fever cases. Diagnosis can then be made sooner or later, according to the developments of the case.

For *relapses* some caution is required in estimating the *dosage* of antitoxin. Although most authorities claim that these are apt to be milder than the original attack, and for that reason feel justified in hesitating to give the antitoxin unless the symptoms are alarming, the author considers that in the face of a genuine second attack of diphtheria a curative dose of antitoxin is in order, since it is the only certain cure at our disposal. It surely represents the minor of the two evils, since the risk of fatal anaphylaxis is so very much less than the effects of the disease, with death as a possibility. The discomfort from the reaction is in no way comparable to the comfort of feeling that a quick cure has been obtained. The author has never observed a fatal or even a serious reaction following a second or spaced injection of antitoxin in the large number of instances in which he has used it.

If every case of diphtheria could be examined during the first twenty-four hours after onset, the treatment could be summed up in two words—**antitoxin, rest**—and the whole course of the disease from first to last could be described in three words, antitoxin, rest, recovery. But unfortunately this is too seldom the case and the general management of diphtheria still requires consideration.

General Management.—For simple faucial diphtheria, if the patient is to be treated at home, the **sick room** should be **large, airy** and as **well ventilated** as possible, the **temperature** being kept at 65° F. (18.3° C.). Hospital patients should be allowed as many cubic feet of air as the circumstances permit. In fact, the author finds **open air** treatment to be as desirable for diphtheria as it is for scarlet fever. During the past two years he has obtained excellent results by placing as many cases as possible, particularly the toxic and the laryngeal ones, in the open corridors day and night during the mild months, while during the severe winter months a room off the ward, known as the cold room, is set apart for these patients. The windows on one side are kept open continuously, the patients being covered and wrapped, with only the face exposed. This treatment is conducive to sleep, and is not only well tolerated, but is often requested by the older children and adults. In certain cases of paralysis of the respiratory muscles it has been known to be a life-saving measure. Absolute **rest in bed** is imperative even for the mildest cases, and for the severe ones it should be continued during convalescence. Owing to the danger of heart complications, absolute rest should be taken to mean the avoidance of all unnecessary movements on the part of the patient. At first no pillow should be allowed, but if this is too irksome one soft pillow may be permitted; at the slightest sign of heart-failure it should be withdrawn, and, if necessary, the **foot of the bed elevated.** In mild cases the patient may gradually be allowed to sit up in bed, well supported by pillows during the third week, and to leave the bed for an hour or two at the beginning of the fourth week. The severe cases in which complications are to be expected should be kept flat in bed for at least five weeks, after which time, in the absence of cardiac or paralytic manifestations, a gradual relaxation of these strict measures may be allowed. But severe cases in which the much feared complications set in must be kept in bed for eight weeks or longer if the complications still persist.

The *diet* during the acute stage should be limited to **liquids, milk, beef-juice, fresh fruit juice** every three hours. **Over-feeding** should be **avoided** in order to prevent vomiting, the strain of which may react on the heart. Difficulty in feeding, which often arises owing to paralysis of the pharyngeal muscles, can be overcome by **nasal feeding** through a **catheter.** The strict regimen of scarlet fever is not called for in diphtheria, so that after the acute stage is passed, as shown by normal temperature, disappearance of local symptoms, and absence of renal involvement, the diet may be cautiously increased to include **stewed fruits, soft-boiled eggs, bread and butter, gelatin, light puddings, gruel, well-cooked cereals,** and can be rapidly followed by a full diet.

MEDICINAL TREATMENT.—There are no drugs that are in any sense specific for diphtheria. Stimulation of some kind is required in all cases during the acute stage. For the mild cases **strychnin** in moderate doses will suffice; the severer ones will require in addition **alcohol,** preferably **whiskey** or **brandy,** and also **caffein; salt solution per rectum** will be found of value in advanced cases. During convalescence **general tonics** will be needed. Some form of **iron** is always indicated, preferably the **syrup** of **iodid** of **iron.**

It is important to keep the **bowels open** in order to avoid straining at stool, or vomiting, both of which may produce collapse owing to the weakened condition of the heart. For the same reason **purgatives** should be **avoided.**

We cannot afford to ignore the function of the kidneys in diphtheria. Although actual nephritis is rare, it is not unknown and must be guarded against by the usual measures for free elimination. In some severe cases of diphtheria with vomiting, the latter may be due to a previous acidosis caused by adrenal exhaustion. For this condition the administration of large doses of **alkali** daily every four hours given at the earliest possible moment is indicated.

The *management* of *laryngeal diphtheria* presents a more complex problem, inasmuch as in addition to the intoxication there is the mechanical obstruction to breathing with asphyxiation as a possibility. Sometimes breathing may be made a little easier by keeping the patient

warmer than in the pharyngeal cases and by the use of **steam** from the **croup-kettle** and allowing **free access of fresh air.** In using steam in the laryngeal cases care should be taken not to exclude the air. A simple canopy with the spout of the croup-kettle so situated as to allow the steam to flow toward the patient's head will be sufficient. Often the patient will show evidence of the relief experienced in placing his head directly in the path of the current of steam. The author does **not advocate** the addition of drugs (medicated vapors) such as **benzoinum tinctura composita** to the steam. They give no better results than ordinary steam.

For the treatment of *dyspnea* **turpentin stupes** applied **to** the **neck** and **upper chest** have proven of great advantage. Relief is often prompt and appreciation is often expressed by the older patients. For the stupes we use **oleum terebinthinæ,** 2 fl. dr. (7.5 c.c.); **oleum olivæ,** 1 fl. dr. (3.75 c.c.), in hot water, 2 pts. (1 liter), mixing it in a two-quart (4-liter) container, from which it is poured into a basin as needed. A piece of **flannel** (about one-half yard) is wrung out of this solution, fluffed, tested as to heat, and then snugly **applied to the larynx and upper chest,** and changed frequently (every few minutes) so as to have the warmth applied continuously. As an emergency measure it will often be found useful to **rub the chest** thoroughly with **camphorated oil,** followed by the application of **hot flannels.** If hot water is not available the flannel can be heated around a kerosene lamp or by any other available means.

Local Treatment.—In the treatment of diphtheria we have the tremendous advantage of possessing a specific which has a direct effect on the local process, so that local treatment is of no great importance. The antitoxin clears the exudate, while other measures are useful mainly in assisting in the separation and hastening the clearing away of particles of membrane, and for their general cleansing effect. All patients who can help themselves should be encouraged to keep the **mouth clean.** Only the blandest solution should be used for this purpose. The formulas prescribed for a mouth wash for scarlatina cases will be found useful. Those who resist this treatment, especially young children, had better be let alone on account of the danger of heart-failure from undue exertion.

For *internal medication,* **ammonium carbonate** and **syrup of ipecac** are sometimes valuable in hastening the separation of the membrane in the laryngeal cases. But should these measures fail, operative interference—**intubation or tracheotomy**—must be resorted to.

Surgical Treatment.—The indications for operative interference are well-marked dyspnea with recession of the soft parts of the chest, restlessness, a weak, rapid pulse, particularly if the symptoms have not yielded to serum and other treatment.

The proper *time* for interference is a matter of judgment gained only by experience. Operation should not be done too early, since manipulation and the possible damage to the soft parts, together with the presence of the tube which acts as a foreign body, may increase the dangers of an already serious condition, a risk which should be avoided whenever possible. On the other hand, if it is delayed too long, the patient may lose strength and be unable to recuperate in spite of the success of the operation.

As to the *choice* of operation. The author believes that intubation is better suited for hospital practice where trained attendants are always at hand than for patients treated at home. However, in a private case in which operative interference is not urgently called for and intubation is done early in order to permit the doctor to leave his patient with a feeling of greater security, not much harm can result before aid arrives in case the tube is coughed up; in the more serious cases there would be a great risk, and therefore tracheotomy is the choice for private practice.

Intubation.—For intubation the patient, in a recumbent position and with the hands down, is placed in a sheet which is securely fastened about him. With the neck and shoulders resting on a pillow or a rolled blanket the head is thrown back and is held by an assistant standing at the head of the bed or table, who at the same time places the mouth-gag in position on the left side of the patient's mouth. The operator then very gently passes the left index finger along the tongue to its base until he feels the epiglottis, which he turns back. The finger then enters the larynx and rests upon its posterior wall, care being taken not to interfere with the proper intake of air. The operator then passes the tube back until its point comes in contact with the left index finger. With the finger as a guide, the end of the tube is then engaged in the larynx, the handle of the introducer is slightly raised and the tube allowed to drop in with very little pressure. The obturator is then disengaged and the tube firmly fixed in position. A string, or better still, a No. 4 banjo wire, is securely looped in the hole at the end of the tube, and allowed to remain in place, being attached to the outside of the patient's cheek by means of adhesive plaster. The string or wire should be drawn fairly taut so as not to cause extubation by the tongue, or the wire may be cut just inside the mouth, leaving the ends resting on the roof of the mouth. When the intubation has been completed the foot of the bed should be elevated to facilitate drainage and thus lessen the possibility of pneumonia. In order to prevent the removal of the tube by the patient himself, his arms should be restrained by the application of light splints. The tube should be taken out in four or five days, especially if the temperature and respiration are normal.

Extubation.—Extubation is simple, provided the tube has been anchored according to the above method, much more simple than when the regular instrument or extubator is used. By drawing the string or wire taut with the fingers of the one hand and passing the index finger of the other hand along the string to the larynx, the tube can be lifted out in a few seconds with practically no disturbance to the patient; where the wire has been cut the end can be grasped with forceps and the tube gently lifted out. The child need not be taken out of bed; indeed, very often the removal can be made during sleep without his knowledge.

In removing the tube, the weather and the time of day should be taken into consideration. The early forenoon of a bright sunny day is the best time to choose, since respiratory difficulties are most apt to occur at night and in damp weather. Sometimes the patients do not do well after extubation and may require the use of steam as above indicated for the relief of dyspnea; but should actual dyspnea set in, re-intubation may be demanded, the tube being again removed in four or five days.

Intubation, as already indicated, should be done only after other efforts have failed to give relief, for the reason that we wish to avoid unnecessary trauma to the soft parts. A tube in the larynx acts as a foreign body, causing increased secretion and retention, which in some instances leads to ulceration. If after the repeated removal of the tube the child is unable to do without it, he should be taken to a specialist after the quarantine has been removed. In the management of tube cases fresh air and a warm sunny room are of great importance.

Tracheotomy.—The technic of tracheotomy for the relief of diphtheritic laryngeal stenosis is the same as for any other similar condition. The patient is wrapped in a blanket or sheet (as for intubation) and the head kept back by placing a rolled blanket, 4 to 5 in. (10 to 12.5 c.) in diameter, under the neck and shoulders; the site of operation is prepared with **iodin. Ether anesthesia** is used, except in emergency and in extreme cases, when no anesthetic will be required.

The operator, steadying the trachea with his left hand, locates the upper two or three rings of the trachea and makes a fairly free incision 4 to 5 cm. (1½ to 2 in.) long. He carefully divides the tissues in the median line (it is of the utmost importance that the incision be made in this line and that the knife does not deviate from it), and is followed up by his assistant, who keeps out of the field the thyroid gland and any vessels that may be present. As the trachea is reached the finger is placed in the wound and two or three rings are cut through with the knife. This is usually followed by violent coughing. The wound should be held open by dilators or by the handle of the knife, held at right angles to the incision until the coughing ceases and breathing seems tranquil and easy. In the meantime a search can be made for particles of membrane, which are removed with forceps. The tube is now inserted and held in position by tape strings placed in the ends of the tube and fastened around the patient's neck. A simple dressing of sterile gauze is placed around the tube and over the wound and is protected from the secretions of the latter by a flap of rubber tissue. Should there be much mucus or hemorrhage the table, or the foot of the **bed,** can be **elevated** to facilitate drainage by gravity away from the trachea and the lungs.

It is sometimes necessary to operate quickly and to plunge right in without all these precautions. This presents no great difficulty provided the median line is kept. Any hemorrhage that results is venous and can be easily controlled.

The tube should not be disturbed as long as the breathing is not interfered with; but in case of any embarrassment to breathing, which may happen owing to the presence of mucus plugging up the tube, it will only be necessary to remove the inner tube and clean it out. The dressing can be changed once or twice every twenty-four hours. The use of steam inhalations will not be necessary if the room is warm enough. Lacking this, the steam from the croup-kettle, so placed as to allow the currents of air to carry the steam to the patient, will be sufficient to moisten the atmosphere and warm the room.

The most dreaded effect of tracheotomy is the development of bronchopneumonia; therefore, a return to normal temperature and respiration is a welcome sign, indicating that the danger is passed. But prognosis is not good if there is a profuse discharge of thick tenacious mucus.

After sufficient time has elapsed to permit the separation of the membrane—from 2 to 4 days—the patient's ability to do without the tube can be tested by plugging the opening. If no embarrassment to breathing results, the tube may be removed and the wound covered with a plain dressing of gauze. It may sometimes be necessary to keep the tube in for several weeks or even months. In the case of nervous children who are apt to imagine that they cannot do without the tube, the test can be made by using a dummy tube, that is, one large enough to fill the wound but not long enough to reach into the trachea. Should the patient show signs of becoming a chronic tube-wearer a specialist should be consulted.

TREATMENT OF COMPLICATIONS.—**Antitoxin,** if given in sufficient amounts and early in the disease, will prevent complications. But should they occur their treatment is the same as obtains when these conditions arise from other causes.

Cardiac symptoms will require **rest,** as nearly absolute as possible, **quiet, fresh air,** the administration of **tonics** and **attention to bowels** and **diet,** as already mentioned. The value of stimulants is sometimes questioned, but we generally give **strychnin** in tonic doses. Cases that present such marked symptoms as syncope, vomiting or precordial pain, may require, in addition to the strychnin, **alcohol, atropin** or **camphorated oil** and **hypodermics of morphia** as a sedative. **External heat** and **raising the foot of the bed** may also be useful in allaying the alarming symptoms. For the vomiting it is best to withdraw all food and medication by mouth, except **champagne,** which is stimulating and can often be retained when other things can not. Any medication should be given either hypodermically or by bowel.

The *paralyses* of diphtheria, like heart-failure, can be absolutely avoided by sufficient and early serum therapy. They are generally transient and will require little treatment except **rest, fresh air,** and perhaps the pushing of **strychnin** internally. The author finds **massage** and **electric treatment** to be **of little avail,** and in fact **dangerous** if applied too early. He believes it best to dispense altogether with such measures.

Where the paralysis affects the muscles of deglutition the **foot of**

the bed should be **elevated** in order to prevent the saliva from collecting, *since it may* cause suffocation or aspiration pneumonia, the patient *actually drowning in* his own secretions. The mouth should be kept free by *gently* **soaking** up the collection of **saliva with gauze sponges. Feeding** *in these* cases is best accomplished **by means of the catheter through the nose.** The bed supports should, of course, be removed during the process.

Bronchopneumonia is treated by placing the patient in the **open air** and the use of **supportive measures** as indicated by the condition when due to other causes.

Nephritis in diphtheria is generally not so serious as in scarlet fever and as a rule yields readily to simple treatment—careful **diet,** free intake of **water, diuretics,** in short, all the measures recommended for scarlatinal nephritis, except the hot pack. This is rarely required, and indications for their use should be carefully considered on account of the risk of aggravating the heart condition by too active treatment.

Otitis, otorrhea and their sequelæ are not the problem in diphtheria that they are in scarlet fever, but treatment is the same as that outlined for the latter. The discharge from the ear may be due to mixed, or even to non-diphtheritic, infection, but the patient should not be considered free from infection until after careful and exhaustive study of the discharge has been made as to its non-infectious character.

Adenitis, likewise, is not a serious complication of diphtheria. It can be treated by **ice-bags** during the first 24 to 48 hours after its onset, and if these are not effective in reducing the swelling **heat** should be tried. Aggravated cases may require **operation** under the same precautions as indicated for interference in cervical adenitis in scarlet fever. Sometimes, however, the deeper glands are involved without involvement of the skin. Indications for surgery would then rest upon the general symptoms such as septic temperature, rapid pulse and the persistence of the swelling.

MANAGEMENT OF CONVALESCENCE.—Owing to the severe anemia and the depressing effects of the disease, the management of convalescence of the diphtheria patient is perhaps of greater importance than that for other conditions. The danger of late heart-failure and the possible development of late paralysis must always be borne in mind. The patient should be kept in bed for at least two weeks after the throat has cleared, and longer if there are any signs of cardiac weakness. The heart action must be carefully watched. The slightest indication of trouble, especially a slow, full, irregular pulse, always demands complete **quiet** and **rest in bed,** in order to avoid the fatal syncope which always threatens in such cases.

After the patient has been pronounced ready for discharge, he should, if possible, **not resume the routine of active life for some weeks after recovery** in order to avoid possible late complications from overstrain on the affected muscles, as, for example, ciliary paralysis or strabismus from reading too much, or other late paralyses.

An annoying problem of diphtheria convalescence is the *carrier* in whom the organism persists in the recesses of the affected parts. This often delays the discharge of the patient when otherwise he is to all appearances cured. It is the author's practice not to pronounce a patient ready to return home until two or three successive cultures have been returned negative, taking into consideration, of course, the duration of illness and the condition of the local parts. The question of discharging patients varies also according to the local laws of health. The favorite sites for the lodgment and retention of the organisms are the tonsillar crypts, the nasopharyngeal adenoid tissue and the nasal sinuses. **Local antiseptic treatment** is sometimes advised but has never proven uniformly effective. In some instances in the case of these persistent carriers, the organism will be found upon inoculation tests to be avirulent, and the patient may be allowed to go home. **Change of air** and an **outdoor life** may materially assist in ridding the body of the organism. But in the very stubborn cases the author finds the only really curative measure to be the appropriate **operation for enlarged or diseased tonsils, adenoids, diseased sinuses, enlarged turbinates** and **septum deformities.** Operation should, of course, be deferred until the patient has completely recovered or at least so far recovered as to render it safe.

Attempts at curing the bacillus carrier by "**over-riding,**" that is, by the use of sprays of other organisms and by intramuscular injections of milk, have been reported favorably from some sources, but their practical value has not been demonstrated.

Prognosis.—The importance of early administration of antitoxin in the prognosis of diphtheria has been referred to several times directly and indirectly in the course of this discussion. While treatment on the first day insures not only a mild course of the disease, with less risk of paralysis, but also recovery in practically all cases, the prognosis grows gradually less favorable with each day that elapses before the first administration of the serum, and becomes dark indeed if treatment is delayed beyond the fourth day.

Much of the prognosis of the disease, of course, depends upon the age of the patient and the previous condition as well as upon the extent of the membrane, the rapidity with which it spreads and the particular type of the disease. Children under two years of age are more apt to develop laryngeal diphtheria, which is the most serious type of the disorder. On the whole, therefore, diphtheria in a child before the third year of life is more dangerous than later in childhood.

As to remote effects, although paralysis is sometimes persistent for a long time, permanent disability is rare, nor is the effect of the toxemia on the heart known to be of a permanent character.

Pathology.—The effect of the diphtheritic organism which finds lodgment in a minute breach on a mucous membrane is seen in the local deposit of a fibrinous exudate, the characteristic clinical feature of the disease. But pathologically the essential lesion is the degenerative and exudative change in the sinuses beneath the affected mucous membranes in which the main effects of the toxin are seen. The changes involve principally the epithelial cells of the mucous membrane concerned, the heart muscles, the lungs, the kidney, liver, spleen, the alimentary canal, the lymph-nodes, the ductless glands, the central and peripheral nervous systems, the bone-marrow and the blood.

The pseudo-membrane is the result of degeneration, necrosis and desquamation of the epithelial cells followed by increasing exudation of fibrin and the gradual formation and increase in thickness of the membrane. Under the microscope the membrane is seen to consist of an interlaced network of fibrin in which are found degenerated epithelial cells and clumps of bacilli, the latter being best observed in the lower and newer layers. Sometimes there is also an admixture of pyogenic cocci, such as streptococcus and pneumococcus. In addition to the local formation of the membrane the bacilli are active in elaborating toxins which are carried by way of the lymphatics and the blood stream from the original point of attack to other locations, from which they continue to give off toxins. The disease, therefore, may also be general as well as local, although there is little doubt but that the "great poison factory" is at the original site of invasion. Destruction of the superficial layers of the epithelial cells opens up avenues for the absorption of the toxins, and the more the local lesion is permitted to spread the more numerous will be the locations liberally supplied with lymphatics that will become affected, and the more pronounced the toxemia that results.

Heart.—The greatest interest in the pathology of diphtheria centers upon the changes in the heart muscle. Councilman, Mallory and Pearce in their study have found some degree of fatty degeneration of the muscular fibers in many of the cases. The degeneration is variable in extent, sometimes affecting the general myocardium and sometimes only special foci. Fatty degeneration is seen along with more advanced forms of degeneration which result in the complete destruction of the muscle. The simple fatty degeneration occurs in severe, short cases, while the prolonged severe cases present more extensive degeneration. The phenomenon is due to the action of the toxin, which clinically manifests itself by the impaired heart function.

Thrombosis may result from primary necrosis of the endocardium.

Lungs.—The lungs are not only very frequently affected by the diphtheria toxin, but at the same time present the most serious lesions met with in the disease. In fact, it is often pulmonary involvement rather than the diphtheria itself which leads to death. The lesions are present in the form of bronchopneumonia, with a fibrinous, hemorrhagic, serous or even entirely cellular exudate. Actual lobar pneumonia is practically never found. Thrombi are occasionally noted in the larger vessels but not in the capillaries. The lymphatics are generally seen to be dilated, containing coagulated albumin, fibrin or cells. They are often found packed with cells and large cells resembling those seen in the air spaces.

Alimentary Canal.—The alimentary canal is rarely the site of pathological changes in diphtheria. In some few cases the stomach presents a definite membrane, which is usually limited in extent, although it has been known to involve the entire gastric mucosa. Very few diphtheria bacilli were found in this membrane by Councilman, Mallory and Pearce, but they appeared abundantly in cultures.

The intestinal mucosa shows few changes except more or less thickening, and some enlargement of the lymph-gland-nodules of the small intestines.

Liver.—The liver presents no gross changes characteristic of the disease; they are the same as those found in other acute infections. The liver is swollen, tense and more or less congested. Microscopically the most constant lesion seems to be the swelling of the cells with increased granulation, especially in the center of the lobules. Sometimes there is fatty degeneration consisting of actual necrosis.

Kidneys.—The changes in the kidneys vary from epithelial degeneration, acute interstitial changes, to a glomerular nephritis; hemorrhage and chronic interstitial lesions are rare. But there is no type of lesion that can be considered typical for diphtheria.

The epithelial degeneration occurs in the larger number of cases and is nearly always the main or the only lesion. It is present in varying degrees and consists of fatty degeneration, hyaline degeneration affecting mainly the convoluted tubules, and the presence of casts. The most constant change is seen in the glomeruli, consisting of a small amount of granular coagulum between the tuft and the wall.

While there seems to be a general agreement between the albuminuria and the degree of degeneration, there is apparently no such correspondence between the character of the degeneration and the general infection with various organisms, such as streptococcus, *Staphylococcus aureus* and pneumococcus, all of which have been found variously associated with the diphtheria bacilli.

The acute interstitial renal changes are generally associated with the more prolonged cases. Interstitial nephritis is evidenced by infiltration of the interstitial tissue with plasma cells; the infiltration, although it involves all parts of the kidneys, is more pronounced in certain foci than in others. The epithelial degeneration varies in different cases. The kidneys are enlarged only in the more pronounced ones.

Pronounced glomerular nephritis is found in only a limited number of cases and generally in the older patients and the more prolonged cases. The first evidence of the change is seen in the increase in cells and proliferation of the endothelium lining the vessels, followed later on by hyaline cellular degeneration.

Spleen.—The most marked features in the spleen are the presence of large phagocytic, epithelial-like cells in the lymph-nodules, and necrosis of the lymphoid cells. The spleen is firm but not distended, smooth, and not markedly enlarged. The lymph-nodes are nearly always distinct and sometimes even prominent.

Nervous System.—The lesions in the nervous system are still the subject of much discussion. Nearly all investigators, however, agree that the changes consist in degeneration due to a toxic parenchymatous and *interstitial neuritis*, some claiming that the condition is purely peripheral, while others show that it may be central, involving the spinal cord. In the peripheral nerves there is usually degeneration of the medullary sheath, which breaks up into globules; the axis cylinders become involved and may rupture crosswise, leading to degeneration of the nerve-fibers below them. The primitive sheath remains intact. Both the sensory and the motor nerves may be affected, but some of the fibers probably remain intact, and the resulting paralysis is then only partial. Baginsky and others have described changes in the anterior cornua of the spinal cord, consisting of atrophy of the ganglion cells, hemorrhage in the gray matter of the spinal cord, degenerative changes in the various peripheral nerves as well as in the anterior and posterior spinal roots, and foci of exudates in the posterior roots.

Involvement of the vessels may lead to emboli with secondary involvement of the nervous system.

There is as yet no agreement as to whether the central or the peripheral nervous system is primarily affected in diphtheritic paralysis, nor has the nature of the changes been sufficiently elucidated to identify them positively as due to lymphogenous infection of the central nervous system. Some investigators attribute the condition to an ascending neuritis along the peripheral nerve centers, as in rabies and tetanus. Others believe it to be due to a lymphogenous infection; while still others, notably Bolton and Bown, do not admit this mode of infection but regard any involvement of the nervous system as part of the general systemic infection carried by the blood stream. Walshe, in what appears to be the most recent study of the question, inclines to the theory of a two-fold mechanism. The early and most characteristic paralytic manifestation, he ascribes to an ascending infection of the central nervous system. The toxin elaborated in the membrane passes up to the medulla in the perineural lymph channel of the cranial nerves, innervating the tonsils and the fauces; but the initial and essential lesion is produced not by the passage of the toxin in the lymph channels, but by its action on the central nervous system, i.e., on the nuclei and nerves involved. The late paralysis is due to the generalized systemic toxemia. Clinically, it resembles a multiple neuritis—its delayed onset appearing simultaneously in all the spinal nerves—and is more lasting in its course than the earlier paralytic symptoms. Walshe thus accounts for the phenomena of faucial and of wound diphtheria, the latter being strikingly illustrated by one of the cases cited, in which a physician, while performing tracheotomy on a diphtheritic patient, had his right thumb infected. The paralysis first localized in the affected member and then became generalized in the spinal nerves, the cranial nerves never having been affected in the slightest degree.

Muscular System.—The muscles also are subject to severe changes. The skeletal muscles show the same fatty degenerative phenomena as are found in the heart and the nervous system where these are involved, but they are perhaps not quite so marked.

Bone-marrow.—The changes in the bone-marrow are not distinctive of diphtheria since it shows the same hyperplasia as is found in other infectious conditions. In experimental diphtheria there seems to be some increase in giant cells and leukocytes to a limited extent, together with nuclear changes in the latter. The red blood-cells remain unaltered.

Glands.—Of the ductless glands the *thymus* was the only one in which Councilman and his associates found any changes. It shows degeneration of the lymphoid cells, generally within the larger cells with vesicular nuclei, most marked in the vicinity of the Hassel bodies.

Blood.—The presence of the toxin in the blood of diphtheria patients is generally acknowledged, while the Schick test demonstrates the presence also of antitoxin in the blood of certain individuals.

The blood-picture in the cases of diphtheria that do not receive antitoxin corresponds to the severe anemia that attends such cases clinically. In the untreated cases the red blood-cells show a reduction of as much as over two million, while of the treated cases only a few present a reduced red blood-count, which is also not nearly so marked. The hemoglobin decreases correspondingly but recovers more slowly than the red blood-cells.

Leukocytosis may or may not be present. According to some authors the leukocytosis, when present, is promptly affected by antitoxin, but only if it is administered during the first twenty-four hours of the disease; the lymphocytes, on the other hand, show an increase after the serum injections. Myelocytes are a bad prognostic sign, especially in the absence of leukocytosis. On the whole, however, the blood is not of much diagnostic value in diphtheria.

Historical Summary.—Diphtheria appears to be one of the various infectious epidemic diseases that was known to very early writers, judging from descriptions found in ancient writings of ulcerative processes in the throat and of a pseudo-membranous deposit on the trachea. Areteus, a contemporary of Galen, in the second century of this era depicted a disease which is highly suggestive of diphtheria. He spoke of a disorder, more common among children than among adults, in which a thick, moist substance formed over the tonsils and which may be superficial and benign, or extensive, malignant and putrid, causing a disagreeable, fetid odor from the mouth. He believed the disease to have been imported from Egypt and Syria and therefore termed it *morbus ægypticus* or *morbus syriacus.* He also mentioned the difficulty in swallowing fluids, which were sometimes regurgitated through the nose, the husky voice, and suffocation, that often led to a rapidly fatal end.

During the fourth century Macrobius described an epidemic of a disease that prevailed in Rome and which to all appearances was diphtheritic in character. After that time little is found in literature concerning such a disorder until it is again mentioned as prevalent in epidemic form during the fifteenth and the following centuries. These epidemics seem to be concerned mainly with the laryngeal type of the disease. Severe outbreaks of this type are reported from Spain and from Italy during the 16th and the 17th centuries, the Spaniards calling it *garrotillo,* while to the Italians it became known as *gulæ morbus.* During the eighteenth century the disease appeared in epidemic form in France (1736), as *angina trachéale;* in England (1748) it was described by Fothergill as "the sore throat with ulcers"; it was reported in Holland in 1745; in 1752 severe epidemics were reported in Switzerland and also in America.

In 1735 Douglas described a peculiar form of sore throat which appeared in certain New England towns and gradually spread westward to the Hudson River about two years later. Douglas' paper, entitled "An Eruptive Miliary Fever, with Anginosa Ulcusculosia," was translated into French and later quoted by Bretonneau. An epidemic in New York, also in 1752, is described by Father Middleton. In 1771 Bard, a physician of New York, published a pamphlet entitled "An Enquiry into the Nature, Cause and Cure of the Angina Suffocative or Sore Throat Distemper," in which he gives a clinical description of a disease which in its essential features suggests diphtheria. After this no accounts of the disease in this country seem to have appeared until the middle of the nineteenth century, when it prevailed in some parts of New York State, being especially malignant in Albany. According to Caldwell (cited by Löffler) Washington was seized with the malady at his home in Mount Vernon.

In 1809 an epidemic of sore throat is reported from Philadelphia and again in 1831, but diphtheria as the cause of death does not appear in the health reports of that city until the year 1860.

From a monograph on a severe epidemic of sore throat published by F. V. Fitzgerald in 1856, it appears that the disease had by that time reached San Francisco and other towns in California.

But the most accurate description of diphtheria is that by Bretonneau (1826) in France, who based his study on epidemics that prevailed in that country from 1818 to 1826. He recognized the specific character of the malady, giving it the name *le diphtérite* (δų ιφθέρα, the skin or membrane). He also regarded the exudate as the only source of infection, and believed that the contagium spread not through the air but by a sort of inoculation from particles of the exudate coming in immediate contact with moist mucous membranes. Bretonneau also bears the distinction of being the first to note that the association of croup and malignant angina was not accidental. Inasmuch as adults who were suffering from malignant angina were able to infect children who then presented typical croup, and that the deposits on the tonsils and the pharynx were the same in both the croup and the angina, he was convinced that the two were dependent on one and the same factor. This, together with observations of points of differentiation between the scarlatinal and the diphtheritic anginose membrane, led him to the further conclusion that although appearing in various forms, diphtheria was a distinct clinical entity.

Bretonneau's main deductions were subsequently confirmed by Trousseau (1828), except that the latter regarded the specific affection of the mucous membranes not as a purely local process, but as part of the course of a constitutional disorder. He therefore substituted the term *diphthérie* for *diphthérite,* a change which Bretonneau accepted because he found that the term *diphthérite* or diphtheritis was being used in a sense different from that intended by him. Trousseau's theory gained a number of adherents, but in the light of our present knowledge, it is, of course, altogether untenable. His work is valuable for the description he gives of the very malignant forms with their destructive processes in the pharyngeal region and the general toxic phenomena.

The question of diphtheria as a distinct clinical entity continued to be a source of controversy for several decades. Though upheld by a number of investigators, it was opposed by so eminent a pathologist as Virchow, who claimed that in croup the membrane is deposited on healthy mucosa, while in diphtheria the exudate develops not only on the surface of the mucosa, but extends into its substance, and that it is this membrane which undergoes interstitial necrosis from lack of nourishment owing to compression of the blood-vessels.

It is interesting to note that the transmissibility of the disease as suggested by Bretonneau received ample confirmation by a number of observations. One of these concerns Herpin, a physician of Tours, France (1843). While he was cauterizing the throat of a diphtheria patient the child coughed up a particle of membrane which settled on the doctor's nose and which he was unable to remove at once. He developed a severe nasal diphtheria, accompanied later by severe paralysis, from which he finally died. An instance of wound diphtheria is reported by Paterson (1866). A farmer who had inserted his finger, on which there was an open wound, into the throat of his child who was suffering from diphtheria, in order to remove an obstruction which had caused a fit of coughing, developed a membranous deposit on the open wound which extended over the entire finger. General symptoms followed. The finger healed in a few weeks, but several weeks afterwards the man developed severe paralysis of the lower, and later of the upper, extremities which persisted for four months. At no time were there any throat symptoms.

In spite of these involuntary inoculations in man, the experimental production of diphtheria had up to this time met with only negative results, although Bretonneau had succeeded in producing a typical false membrane in the trachea of dogs by injecting a mixture of cantharides and olive oil. On the supposition that croup was caused by the inspiration of acrid, irritating substances other investigators had previously introduced acids, alcohol and other caustic substances into the air passages of animals with the idea of producing a membrane. Delaford tried chlorin, corrosive sublimate, arsenic, sulphuric acid and ammonia. He found the latter the most suitable for these experiments, and this substance was later employed by others, notably Oertel (1871), in their experiments. But Bretonneau recognized that the resemblance of the artificially produced membrane to the idiopathic one was more apparent than real, since they differed so entirely in their clinical behavior. This observation was subsequently confirmed by Lichtheim in 1883.

The introduction of bacteriology into the arena of medical research was destined to solve the question that had been so diligently pursued since Bretonneau's classic work first appeared.

Before the true causative agent of diphtheria was finally discovered, attempts had been made to establish a relationship between certain fungi and the diphtheritic membrane. In fact, as late as 1881 Talamon described in detail a fungus which he had constantly obtained from cultures, and inoculations of which produced thick, false membrane in animals, especially in the pigeon. But the fallacy of this theory was demonstrated by Duclaux.

In 1868 Huerter, and also Oertel, found small, round, rod-shaped and corkscrew-like, motile bodies in the blood as well as in the membrane and lesions of diphtheria patients, to which they ascribed a certain etiological relationship to the disease. Similar bodies were also subsequently observed by von Recklingshausen, Waldeyer, Nassiloff, Klebs, Eberth, Heiberg and others.

Although these investigators probably had observed the specific organism, they failed to differentiate it from the other bacilli present, a distinction which belongs to Klebs of Zürich (1873). There is a general impression that Klebs' discovery was not made until 1883, but at a Congress held at Wiesbaden ten years before that date he had not only announced his discovery of the diphtheria bacillus, but had also succeeded in obtaining it in cultures. The requirements of Koch for the specificity of a microörganism, i.e., that it must be found constantly arranged in a characteristic manner in the parts involved, that it must be isolated and obtained in pure culture, and that by inoculation into animals the disease must be reproduced in the latter, had not yet been fulfilled. Investigations of the subject were studiously carried on following Klebs' announcement. In 1883 Klebs, at the Congress at Wiesbaden, gave an account of his most recent researches and described in great detail the organism he had isolated as the diphtheria bacillus. In the same year Huebner endeavored to satisfy Koch's third postulate by experimental work. He attempted to produce an artificial diphtheritic exudate in the bladder of the rabbit by mechanical means, and to induce a general disease in other animals by the inoculation of the membrane. Although the animals died from an acute infection with extensive lesions of the bladder, and the infection was transmissible to other animals by inoculation of particles of the mucous membrane of the bladder, the organisms—micrococci arranged in short rods or chains—were found only in the vessels. Huebner, not being able subsequently to demonstrate these same organisms in the vessels of the affected mucous membrane of human subjects dying of diphtheria, concluded that these bacteria in the membranes were saprophytic and that the organism of diphtheria had not yet been found.

Löffler in 1884, however, satisfied all of Koch's postulates and, confirming Klebs' original discovery of the specific organism, he succeeded in producing the disease in the pigeon and in the calf. With the discovery of the Klebs-Löffler bacillus as the causative agent of diphtheria and the new trend of bacteriology toward the study of infection and immunity, investigations were directed to the study of the specific toxin and of the disease and immunization against it.

Roux and Yersin (1889-1890) directed attention to the capacity of the diphtheria bacillus to produce a soluble poison and to the fact that this power could be increased or diminished by cultivation on suitable media. Von Behring and Ehrlich later successfully pointed out the possible estimate of the strength of the diphtheria toxin, and their work was then followed by the studies of numerous investigators with regard to the behavior of the toxin in solutions and its method of action upon the constitution.

Local treatment of diphtheria by means of antiseptics with a view to preventing the formation of the membrane was at this time receiving great attention, but the conclusion was soon reached that these were of little value. Von Behring, in the course of his therapeutic studies, was led to believe that the main object of treatment must be directed toward neutralizing the poison of the diphtheria organism. In 1890 Fraenkel and von Behring began work on artificial immunization against diphtheria. Fraenkel worked in the direction of obtaining immunization by means of injections of large amounts of broth cultures of the diphtheria bacillus heated to 65° C., while von Behring followed the lines indicated by experiments with chemical substances. He inoculated guinea pigs with diphtheria cultures which he immediately followed with therapeutic efforts at minimizing the induced disease by injections of iodin trichlorid solutions, repeated for three days after the original inoculation. The animals thus treated survived while the controls died. The surviving animals also exhibited a greater resistance to infection than normal animals, two of them withstanding injections of virulent diphtheritic bacilli which killed controls in 36 hours. Von Behring described this resistance as similar to "the acquisition of immunity in man after convalescence from many infective diseases."

Thus the foundation for immunization against diphtheria was laid. Subsequent investigations by von Behring and others have brought the method to its present perfection. The benefit to mankind of this discovery can hardly be estimated. It remains only for the general practitioner to make use of the method on every occasion at the first indication of throat trouble in order to bring about the day when diphtheria, instead of being one of the ordinary, will be one of the extraordinary diseases of childhood, and of mankind in general.

BIBLIOGRAPHY

Babonneix, L. Les paralysies ascendantes aiguës dans le diphthérie experimentale. Arch. gén. de méd., 1903, ii, 3201.

Baginsky, A. Diphtherie und diphtheritischer Croup. Vienna and Leipzig, 1913.

von Behring, E. Ueber ein neues Diphtherieschutzmittel. Deutsch. med. Wchnschr., 1913, xxxix, 873.

Bolton, C., and Bown, S. H. The pathological changes in the central nervous system in experimental diphtheria. Brain, 1907, xxx, 365.

Bolton, C., and Brewer, D. A case of extensive cutaneous diphtheria with an examination of the nervous system. Lancet, 1905, i, 1130.

Bretonneau, P. Traité de la diphthérite. Paris, 1826.

Brieger, L., and Fraenkel, C. Untersuchungen über Bacteriengifte. Berl. klin. Wchnschr., 1890, xxvii, 241.

Carey, B. W. Lessons from a study of one thousand diphtheria deaths. Boston Med. and Surg. Jour., 1919, clxxx, 67.

Crawford, A. C. Chemistry of diphtheria antitoxin. Am. Jour. Pharm., 1918, xc, 765.

Conradi, H., and Bierast, W. Ueber Absonderung von Diphtheriekeimen durch den Harn. Deutsch. med. Wchnschr., 1912, xlviii, 1580.

Councilman, W. T., Mallory, F. B., and Pearce, R. M. Diphtheria: study of the bacteriology and pathology of 220 fatal cases. Boston, 1901.

Graham-Smith, G. S. The diphtheria bacillus: in The bacteriology of diphtheria. Edited by Nuttall, G. H. F., and Graham-Smith, G. S., Cambridge, England, 1908.

Holt, W. E. Diseases of infancy and childhood. New York, 1916.

Ker, C. B. Infectious diseases. London, 1909.

Klebs, E. Ueber Diphtherie, ihre parasitäre Natur, etc. Cong. f. Innere Med., Wiesbaden, 1883, ii, 125.

Kolmer, J. Contributions to the bacteriology of diphtheria. Jour. Infect. Dis., 1912, xi, 56.

Löffler, F. Untersuchungen über die Bedeutung der Mikroörganismen für die Entstehung der Diphtherie bei Menschen, bei der Taube und beim Kalbe. Mitt. a. d. k. Gesundheitsamt, 1884, ii, 451. Centralbl. f. Bakteriol., 1887, ii, 105.

——— History of diphtheria: in The bacteriology of diphtheria, edited by Nuttall, G. H. F., and Graham-Smith, G. S., Cambridge, England, 1908.

Mondolfo, E. Criteri diagnositici profilassi e terapia delle difterite. Pisa, 1915.

Park, W. H. Antitoxin administration. Boston Med. and Surg. Jour., 1913, clxviii, 73.

——— Practical immunization against diphtheria. Med. Record, 1918, xciii, 615.

Immunization of infants against diphtheria. New York Med. Jour., 1918, cviii, 221.

Park, W. H., and William, A. W. Pathogenic organisms. New York and Philadelphia, 1917.

Park, W. H., and Zingher, A. Active immunization with diphtheria toxin-antitoxin, and with toxin-antitoxin combined with diphtheria bacilli. New York, 1916.

Paschen. Versuche mit paraënteralen Milchinjektionen zur Entkeimung der Keimträger bei der Diphtherie. Deutsch. med. Wchnschr., 1918, xliv, 367.

Paterson, A. H. Case of diphtheria by inoculation appearing on a wound without the corresponding affection of the fauces, and followed by paralysis. Med. Times and Gaz., 1866, ii, 608.

Peters, B. A. Acidosis as a possible cause of certain symptoms in diphtheria. Brit. Med. Jour., 1918, i, 10.

Peters, J. C. Notes on the early history of diphtheria in the United States. W. Virginia Med. Student, 1876, i, 254, et seq.

Roux, P., and Yersin, A. Contribution à l'étude de la diphthérie. Ann. de l'Inst. Pasteur, 1888, ii, 1629; 1889, iii, 273; 1890, iv, 385.

Sanford, A. H. Diphtheria bacillus carriers treated with cultures of lactic acid bacilli. Collected papers, Mayo Clinic, 1914, v, 35.

Schick, B. Die Diphtherietoxin Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheilseruminjection. München. med. Wchnschr., 1913, lx, 2608.

WALSHE, F. M. R. Post-diphtheritic paralysis following cutaneous diphtheria. Lancet, 1918, ii, 232.

——— On the pathogenesis of diphtheritic paralysis. Quart. Jour. Med., 1918, xi, 191.

WEAVER, G. H. The virulence of diphtheria bacilli from diphtheria patients and diphtheria carriers. Jour. Infect. Dis., 1917, xx, 125.

WELCH, W. W., AND SCHAMBERG, J. Acute infectious diseases. Philadelphia, 1905.

WESTBROOK, F. F. Problems in the laboratory study of diphtheria. Reports Am. Pub. Health Assn., 1903, 381.

WOODY, S. S. Intramuscular injections of antitoxin. Penn. Med. Jour., 1915, xix, 176.

WOODY, S. S., AND DACOSTA. Diphtheria: in Handbook of medical treatment. Philadelphia, 1918, i.

WRIGHT, L. T. The Schick test with special reference to the negro. Jour. Infect. Dis., 1917, xxi, 265.

ZINGHER, A. Immunization of infants against diphtheria. Am. Jour. Dis. Child., 1918, xvi, 83.

CHAPTER VIII

ERYSIPELAS

By H. B. Cushing, M.D., C.M.

Definition, p. 177—Etiology, p. 177—Predisposing causes, p. 177—Exciting cause, p. 178—Symptomatology, p. 178—Clinical history, p. 178—Diagnosis, p. 179—Complications and sequelæ, p. 180—Association with other diseases, p. 181—Clinical varieties, p. 181—Treatment, p. 182—Prophylaxis, p. 182—General management, p. 182—Local treatment, p. 183—Specific therapy, p. 183—Prognosis, p. 184—Pathology, p. 184—Historical summary, p. 185.

Definition.—Erysipelas is also called, locally, "the Rose" and "St. Anthony's Fire." It is a contagious disease, characterized by a peculiar inflammation of the skin or, more rarely, of the mucous membranes, with constitutional symptoms. It is due to a specific microörganism, the *Streptococcus erysipelatis*. The infective organism remains local, the general symptoms being due to absorption of toxins and not to septicemia.

Etiology.—Erysipelas is endemic in most communities. It is seldom seen in the epidemic form at the present time, and probably epidemics only occur from overcrowding, neglect of proper ventilation and aseptic precautions in hospitals.

Sporadic cases may occur at any time or place with no evident connection with one another. Probably many healthy persons act as carriers, the streptococci only being virulent under special circumstances of individual susceptibility and the presence of an entrance wound. Certainly, persons suffering from repeated recurrent attacks must perpetually carry the organism in their body.

PREDISPOSING CAUSES.—The predisposing causes are overcrowding and poor sanitation, also debility from chronic alcoholism or chronic wasting disease. Individual susceptibility apparently plays an important part. Wounds, slight traumatism or recent confinement also obviously predispose to the disease. Little importance can be placed upon age, infancy and old age being equally susceptible. The most frequent occurrence is between the ages of 35 and 55.

A variation in frequency according to season has been noted by some observers, there being an increased number of cases in the spring and fall months. Probably this is to be explained not by changes in the temperature or atmospheric conditions at these seasons, so much as by the habits of the population as to overcrowding and lack of open-air exercise.

Exciting Cause.—The exciting cause is a streptococcus first described by Fehleisen as *Streptococcus erysipelatis.* It is apparently a special strain of the *Streptococcus pyogenes* and indistinguishable from it morphologically or by cultural peculiarities. It is readily found in the lymph-spaces at the spreading margin of the lesion and easily cultivated on ordinary culture media. It is easy to demonstrate the disease by inoculation of cultures into the ear of a rabbit, and it has often been produced in man by inoculation, this experiment being carried out for the cure of chronic skin diseases, such as rodent ulcer or sarcoma.

In ordinary cases the streptococci remain localized in the skin lesion, but in exceptional cases they may be cultivated from the blood or found in the various organs of the body. The organism is probably conveyed from one patient to another, by contact infection, especially by means of the hands of attendants. It gains access to the body through some wound or abrasion, which may be so slight as to escape notice, or may heal during the incubation period of the erysipelas. The fact that the disease on the face usually starts at the margin of skin and mucous membranes, where excoriations are frequent, supports this view.

Symptomatology.—Clinical History.—*Period of Incubation.*—The incubation period is short, 2 to 8 days, most commonly 3, and is characterized by no symptoms. When the disease is experimentally produced in man, as has been done for the treatment of incurable tumors, the incubation period is 15 to 61 hours.

Mode of Onset.—The onset is abrupt with a sharp rise of temperature. There is usually a chill, often as severe as in the onset of pneumonia. Occasionally, in children, the onset is with a convulsion. Vomiting frequently occurs, but not always. The local lesion is usually to be noted simultaneously with or very shortly before the general symptoms.

Course.—The symptoms of the disease fall naturally into two groups: (1) those due to the local lesion, and (2) the constitutional symptoms.

(1) *Local Symptoms.*—The local lesion in 90 per cent. of the cases is situated on the face, beginning usually at the nostril or bridge of the nose, occasionally on the lip or external auditory meatus. The next most common site is in the leg, in about 8 per cent. of the cases, usually starting from some abrasion or sore, but the disease may also start in any wound or abrasion of any part of the body. A sharply defined patch of redness appears on the skin. This is raised, hot, swollen and shiny, and accompanied by a feeling of burning or tension. It gradually spreads by direct continuity to surrounding areas. The margin of the patch is most characteristic. It is raised, palpable, usually irregular in outline. It progresses steadily, and its gradual advance may be noted from hour to hour. The surface of the area involved is usually smooth and shiny, occasionally marked by small vesicles or blebs containing clear fluid. As the margin advances, the original area becomes gradually less swollen and the redness fades. The inflammation lasts in a particular spot for three or four days so that the disease may still be spreading in other parts when the original focus has become normal. When the

disease spreads over loose tissues, there is great edema of the parts. The eyelids, in particular, become so swollen that the eyes are closed; the ears may become greatly thickened, and at times the natural wrinkles of the face may become obliterated. As the inflammation subsides, the skin is left somewhat discolored and usually desquamates either in branny scales, or more rarely in sheets. The vesicles or blebs soon break and dry up, leaving adherent crusts. They occasionally become purulent and may leave shallow ulcers, sometimes causing a superficial gangrene. The nearest lymphatic glands are almost invariably enlarged and tender.

The inflammation may attack the various mucous membranes either primarily or by extension from the skin, causing the same redness and swelling of the surface, but the appearance is not so characteristic. The nose is frequently entirely occluded, resembling an attack of acute coryza; the tongue may be extremely swollen, filling up the mouth; and the throat also may be attacked, causing edema and swelling of the soft palate and uvula. In exceptional cases, the disease may extend to the larynx, when one is apt to have rapid and fatal edema of the glottis. When the scalp is attacked, redness is not seen, but the area involved may be outlined by the marked swelling and edema. There is usually greatly increased pain and headache in these cases.

(2) *Constitutional Symptoms.*—Fever is the most noticeable and characteristic symptom. It is usually fairly high and continuous the first three or four days, becoming then more intermittent. It most often terminates abruptly by crisis, but this is rarely as abrupt and defined as in pneumonia, and frequently takes the form of a rapid lysis, for a period of two or three days. Occasionally, the fever is intermittent or septic from the first or, in some cases, the fever is low and may even be entirely absent. Delirium is common and there is often severe headache and anorexia; but, as a rule, the subjective symptoms of the fever are less marked than one would anticipate from the height of the temperature. Cases of so-called "wandering erysipelas" give an irregular fever lasting several weeks, an increase of fever usually being associated with a fresh local outbreak. The pulse is rapid, respiration slightly increased, the skin usually hot and dry, although in many cases sweating is coincident with the remissions of temperature. The urine is diminished and febrile in character, and a febrile albuminuria is almost constant. The spleen may be enlarged in severe cases. There is often present a functional cardiac murmur. Leukocytosis is practically constant and may reach a high degree.

Diagnosis.—There is no difficulty in diagnosing the ordinary case of facial erysipelas. The characteristic appearance of the local eruption, especially of the sharply-defined, raised, advancing margin, the presence of vesicles on the surface and the inflammation of the neighboring lymph-glands, are usually quite distinctive. The combination of this lesion with the sudden onset of constitutional symptoms and high fever forms a picture unlike any other disease with which we have to deal.

Cases of erysipelas without fever frequently occur, especially in recurrent attacks and in persons suffering from some other debilitating disease. The character of the local lesion, however, remains unchanged and should readily establish the diagnosis.

Erysipelas of the mucous membranes of the nose or throat presents exceptional difficulties; an acute spreading inflammation associated with severe constitutional symptoms might arouse suspicion, but the diagnosis is rarely established until the characteristic involvement of the skin occurs.

DIFFERENTIAL DIAGNOSIS.—A *diffuse cellulitis* causes the most frequent difficulty, or the inflammatory edema extending from a *carbuncle*, a local *anthrax* or a *furuncle* in the nose. In all these cases there is more brawny induration, absence of the characteristic, ridge-like margin and of the definite constitutional symptoms. Again, erysipelas tends to heal in the center and spread peripherally, which eventually clears up the diagnosis.

Herpes of the face, especially *herpes frontalis*, may cause confusion for a time, but the sharp limitation to an area supplied by a branch of the trigeminal nerve and the differences in the character of the lesion soon clear up the question.

Acute eczema and *dermatitis*, e.g., that caused by primula poisoning, has occasionally caused mistakes, but the absence of constitutional symptoms and the fact that these diseases spread by the coalescence of small pinpoint lesions and never present a distinct raised margin, should obviate the difficulty.

Complications and Sequelæ.—*Abscess* formation is by far the most common and important of the complications, occurring in nearly 10 per cent. of all cases. The abscesses are sometimes superficial, arising from suppuration of the vesicles or blebs which are so common in the disease, and sometimes are more deep-seated, as in the subcutaneous tissues. Certain types of the disease and certain outbreaks or epidemics appear particularly liable to be associated with abscess formation.

Sometimes the inflammation leads to *superficial gangrene* or sloughing, especially over the ears, the tip of the nose, the ends of the toes and fingers. If the erysipelatous inflammation extends over the sacral region, it is almost certain to cause a bedsore.

Although the streptococci usually remain local in the lymphatics of the skin, they occasionally give rise to a *septicemia* or *pyemia*, and, as a result, abscesses in various organs, pericarditis, empyema and some of the most malignant cases of ulcerative endocarditis occur.

Again, the inflammation may spread locally, causing suppurative adenitis, suppurative arthritis, otitis media, mastoiditis and purulent meningitis. Periostitis, especially of the skull, has been noted in a number of instances.

The extension inward to the mouth and throat occasionally gives rise to edema of the larynx, bronchitis and pneumonia. Pneumonia may also arise from pyemia or from hypostatic congestion as in any severe fever—it is often streptococcal in origin, but sometimes due to other organisms.

Albuminuria is almost constant during the febrile stage and occasionally a true, acute nephritis occurs.

Relapse is not uncommon, especially slight flare-ups of fever with local extension of the disease, after it has been apparently arrested, and there is often noted a tendency to recurrence of the disease after a few weeks or months of immunity. These recurrences are apparently due to persistence of the streptococci in the tissues; they always occur in the same site, and are especially common if some pathological lesion, such as a chronic sinus, persists.

Repeated attacks may leave a thickened, unsightly condition of the skin, a sort of chronic edema, closely resembling elephantiasis.

Involvement of scalp usually leads to alopecia, but the hair grows in again after a short time, unless the attacks are repeated.

Chronic skin diseases, such as lupus, eczema, rodent ulcer and sarcoma, are often benefited and even cured by an attack of erysipelas, and some have gone so far as to inoculate the disease for the cure of such conditions, but this is not considered justifiable.

Association with Other Diseases.—Erysipelas in the past was always associated with wounds and operations, becoming epidemic in hospitals, and it was regarded as one of the dangerous complications which might follow any operation. Since the days of antisepsis, this association has become rarer until such a complication is practically unknown, though surgeons have a wholesome fear of the disease because of its past reputation.

It is still seen, however, complicating infected wounds and particularly arising from such lesions as ulcerating cancer, chronic sinuses or even ulcerating hemorrhoids.

Similarly, aseptic methods have banished it from modern maternity hospitals, but careless midwifery occasionally still leads to the almost uniformly fatal form affecting parturient women, and the equally fatal infection of the umbilicus in new-born infants.

Cachectic states seem to predispose to the disease, and it is not uncommonly seen in the very aged, and in persons suffering from chronic alcoholism. Needless to say, it is such cases which increase the mortality rates in hospitals. In such cases it usually arises idiopathically, i.e., there is no history of exposure to other cases of erysipelas.

Clinical Varieties.—Erysipelas is an unusually variable disease, and a number of distinct types are described, though all are due to the same infective agent.

MIGRATORY ERYSIPELAS.—Migratory erysipelas begins like an ordinary attack, but instead of terminating in the usual time, lasts for several weeks, the eruption gradually spreading to all parts of the body, and even recurring in some localities. This form is commoner in young children, and usually ends favorably in spite of the weakness and prostration from the long-continued fever.

SURGICAL ERYSIPELAS.—This form of erysipelas, originating from a wound, is fortunately rarer in these days of asepsis; it is still occasionally seen in the case of operations on infected areas, e.g., after mastoid operations or operations on chronic osteomyelitis. It is worth remembering that the first appearance of the erysipelatous rash may arise several centimeters distant from the wound or point of entrance.

RECURRENT ERYSIPELAS.—Recurrent erysipelas is not uncommon, especially in cases where there is a chronic discharging sinus or infective lesion in the air cavities of the skull. The recurrences take place, as a rule, every few months and always affect the same area. The constitutional symptoms become less with each attack until they may be absent altogether.

ERYSIPELAS OF THE NAVEL.—This condition occurs in new-born infants where proper aseptic precautions have not been taken with the cord and is almost uniformly fatal.

AFEBRILE ERYSIPELAS.—This form is frequently seen in aged or debilitated persons, or in those suffering from some chronic disease, such as diabetes or nephritis. The prognosis is very grave except in the afebrile cases due to recurrent attacks.

CELLULOCUTANEOUS ERYSIPELAS.—This title is given to a type of the disease tending to involve the deeper tissues and cause abscess formation. This type is apparently due to a special strain of organism and is characteristic of certain epidemics.

Treatment.—PROPHYLAXIS.—Erysipelas is a contagious disease, conveyed by contact infection. It may be carried by the hands of a third person, as, for example, a nurse or doctor. The patient, therefore, should be **isolated** during the attack and the ordinary precautions of disinfection taken, especially the frequent **sterilization** of the hands of the attendants. With the most ordinary precautions there is little danger of infection, even if a patient is treated in an ordinary general hospital.

In the past, fatal epidemics in crowded and unsanitary hospitals, where aseptic precautions were not carried out, have given an unduly bad reputation to the disease. However, cases of erysipelas should never be treated in the vicinity of surgical or maternity cases or by those in attendance on such cases.

The infection does not appear to be a persistent one, in connection with rooms or clothing. Thorough cleansing gives sufficient disinfection. In the case of the patient, the organism may persist a long time, especially if any chronic lesion, such as a persistent sinus or nasal discharge, is left. The period of isolation is usually determined by the healing of the local lesion.

GENERAL MANAGEMENT.—The general management is that of any acute febrile disease necessitating absolute **rest in bed**, abundance of **fresh air, a light but nutritious diet** with an increased amount of **fluid.** The bowels require attention by **enemas** or repeated mild **purgatives,** and the skin should be kept active by regular **sponge baths.**

The fever is apt to be high, but as the course of the disease is short and toxemia not usually marked, it rarely requires special attention. If there is much toxemia and delirium with high fever, **hydrotherapy** gives the quickest and most efficient relief. This is best administered in the form of the cold pack, cold sponging or an alcohol rub, though a regular cold bath may be used in severe cases. If there is continued delirium, and want of sleep, it is better to use an occasional dose of **morphin.** If no cardiac weakness is present, a dose of **veronal** and **phenacetin,** each 5 grains (0.324 gram), will often secure a night's rest.

In cases of severe prostration or threatened cardiac failure, **stimulants** may be employed, but, unfortunately, are as ineffectual as in other acute febrile diseases. **Alcohol** should always be given to those who are accustomed to its regular use; **strychnin, caffein** and **digitalis** have also been advised to tide over the patient until the crisis occurs.

LOCAL TREATMENT.—Local applications have been advised in great profusion. Except for the relief of local distress, the feeling of tension, burning or itching, it is doubtful if they have any effect on the outcome of the disease. Probably **cold compresses** of either **ice-water** or evaporating **lead lotion** give the most relief. Tucker advises the use of a saturated solution of **magnesium sulphate.** Some patients get more relief from the use of a soothing ointment, such as **carbolated vaselin, zinc ointment** or an ointment containing **bismuth salicylate or calamin.** All these are best applied by means of a **mask,** or **dressings of lint.** For many years **ichthyol** in 20 per cent. to 50 per cent. solution or ointment had a great vogue, but it does not appear to give more relief than other applications of more agreeable odor and appearance. The application over the lesion of strong antiseptic solutions such as **iodin, carbolic acid** or **corrosive sublimate** cannot be too strongly condemned, as increasing the distress and risk of the patient without shortening the course of the disease.

Erysipelas is a local infection, spreading peripherally through the lymphatics of the skin, and it is quite possible to arrest its progress in selected cases and bring about an early abortion of the disease by establishing a barrier in advance of the lesion. The method should only be used when the medical attendant is prepared to give personal supervision to the case and see that an effective barrier of aseptic inflammation or compression is produced, entirely surrounding the lesion. This is best done by painting on a band of **liniment of iodin** one-half to an inch wide, about an inch in advance of the lesion and entirely surrounding it. This should be repeated in 12 hours and any sign of breaking through controlled by a fresh barrier farther out. A strong solution of **silver nitrate** has been used for the same effect. Others have advised the use of a strip of nonflexible **collodion** applied in the same way and painted on repeatedly so as to produce a trough-like depression with compression of the lymphatics. The method is innocuous, and well worth trying where the lesion is small and can be entirely surrounded.

SPECIFIC THERAPY.—Hamilton Bell, in 1851, advised the use of **tr. ferri perchloridi** in large doses, 1 to 2 drams (3.75 to 7.50 c.c.) a day, for the treatment of erysipelas, and for sixty years the use was continued. No explanation was ever given of its supposed action and the best authorities unanimously condemn it as irrational and apt to irritate the digestive system of the patient. **Quinin** in doses of 20 to 30 grains (1.3 to 2.0 grams) per day has also been widely used with as little justification or beneficial effect. **Collargol injections** have also been advised as in septicemia, but there is little evidence in favor of the treatment.

The use of **streptococcus vaccines** in large and repeated doses, 100 to 500 million, repeated every day or second day, also has its advocates. It may be of value in protracted cases and probably has some effect in preventing recurrences in patients unusually susceptible to the disease.

The administration of **antistreptococcic serum** seems to offer more hope and is strongly advised by some authorities. It should be given in large doses and frequently repeated. Some cases appear immediately arrested and others not affected at all by the treatment. Possibly a variation in the strain of the organism may have something to do with the effect. A polyvalent serum should be used.

Prognosis.—Erysipelas in the sporadic form, as seen in ordinary practice at the present time, is an almost benign disease. Although the high fever, delirium and repulsive disfigurement would incline one not accustomed to the disease to a grave prognosis, the fact is worth remembering that, in the absence of other disease or complicating condition, the outlook is entirely favorable. The total mortality at first might incline one to doubt this optimism, as it varies from 5 to 10 per cent. in different series of cases. A closer investigation of the fatal cases, however, shows that they are almost entirely comprised of certain types of the disease. Erysipelas of the new-born is almost uniformly fatal. Wound erysipelas, as seen in the epidemic form in former war hospitals, was an appallingly fatal disease, and accidental erysipelas infecting wounds is still a serious affection. The form occurring in cachexias, as in cancer, chronic nephritis, senility, etc., also swells the mortality lists. The cellulocutaneous form with abscess formation gives a higher percentage of deaths. On the other hand, recurrent attacks are progressively less serious, and finally cause little constitutional disturbance.

Even the migratory form, where the fever lasts for weeks and the whole body is involved, usually resolves eventually without bad effects. It is surprising how much of the skin of the body may be inflamed, such an extent of surface as would be uniformly fatal in burns and scalds, and yet the patients do very well.

Unfavorable symptoms are the tendency to abscess formation or gangrene, and evidence of serious involvement of the heart or lungs. As a general rule, an afebrile course shows a lack of reaction on the part of the patient, and, with the exception of a few very mild or recurrent cases of erysipelas, most cases without fever end fatally.

An attack of erysipelas usually leads to complete recovery, no residue or defect being left. Occasionally, however, especially in repeated attacks, there remains a chronic thickening of the skin or lymphatic edema, which may cause disfigurement or disability closely resembling elephantiasis; happily this condition is rare. Permanent effects may also be left in exceptional cases in the form of endocarditis or chronic nephritis.

Pathology.—In the cadaver, the redness of the lesion disappears and there is left only a slight edema. Microscopically, the condition is one of edematous dermatitis, with little fibrinous exudate and only moderate infiltration with leukocytes. There is infiltration of the cutis and subcutaneous tissues with serous fluid containing only a small amount of fibrin. The layers of the epidermis frequently become separated by serum-forming vesicles. Toward the margin of the lesion, the streptococci are found in great numbers in the lymphatic spaces, in the channels at the base of the papillæ, and in the crevices of the derma.

The internal organs in an ordinary case show only the changes associated with an ordinary sepsis, i.e., cloudy or hyaline degeneration.

In cases with secondary infection, one may find evidences of pyemia, malignant endocarditis and septic infarcts in the organs. As noted elsewhere, suppurative inflammation of the various serous membranes may occur, meningitis, pericarditis, empyema or arthritis.

Nephritis, if found, is usually of a degenerative type, or an exacerbation of a chronic nephritis. Occasionally acute septic nephritis may be seen.

Historical Summary.—Erysipelas has been recognized for centuries, but was formerly confused with acute eczema and all diffuse phlegmonous inflammations. Its contagious nature was first recognized about 1850 by English writers. Later Velpeau, in France, and Wernher (1862) and Volkmann (1869), in Germany, emphasized the same fact.

The specific organism was first described by Fehleisen of Berlin in 1883, and later experimental researches confirmed his findings.

The recognition of the contagious character of the disease and its tendency to cause outbreaks in surgical and maternity wards has led to its exclusion from most general hospitals, while most contagious hospitals make no provision for its care. As the infection is not ordinarily virulent, and easily controlled by simple precautions in nursing, there seems no reason why it should not be treated in separate rooms of an ordinary hospital, as typhoid, tuberculosis, syphilis and similar diseases are treated.

CHAPTER IX

VARIOLA

(*Small-pox*)

By Samuel Sidney Woody, M.D.

Definition, p. 187—Etiology, p. 187—Predisposing causes, p. 187—Exciting cause: the organism, p. 188—Modes of conveyance, p. 189—Symptomatology, p. 189—Clinical history, p. 189—Diagnosis, p. 193—Complications, p. 197—Clinical varieties, p. 197—Treatment, p. 200—Prophylaxis, p. 200—General treatment, p. 202—Serum therapy, p. 206—Prognosis, p. 207—Pathology, p. 207—Historical summary, p. 209.

Definition.—Variola, or small-pox, is a highly communicable, acute, specific infection characterized by a rather constant incubation period, sudden onset with high initial fever and marked constitutional disturbances lasting three to four days, followed by an eruption which begins as papules and passes into vesicles, pustules and crusts; and by a secondary rise of temperature during the pustular stage of the eruption.

Etiology.—PREDISPOSING CAUSES.—*Climate.*—Before the introduction of vaccination, small-pox was one of the most prevalent and destructive scourges with which mankind was afflicted, destroying countless lives every year. There is no part of the world in which variola is not known, so that it cannot be said to be influenced by climatic conditions.

Season.—Seasonal influences are apparent in the fact that it is more prevalent in cold weather and that epidemics that break out in the spring and summer months are apt to be less extensive than those that appear in winter.

Age and Sex.—All human beings, irrespective of age or sex, are susceptible to the disease. Infants do not exhibit the natural immunity that they generally show toward infectious diseases. They are known to have been infected *in utero,* but only when the mother herself has had the disease during pregnancy, and may at birth present the rash or scars of the rash. As a rule, however, the fetus is not affected and a child born in a small-pox hospital, if vaccinated at once, may escape the disease.

Race.—As to race, there seems to be a general impression that colored people are more susceptible than are white people. This would apparently be substantiated by the fact that negroes are decidedly in the majority among the variola patients of a hospital for contagious diseases. But on second consideration it is more likely to be due to social and educational conditions, inasmuch as small-pox generally arises among the poorer classes, where the evils of over-crowding are active, especially more so during the winter than during the summer when the windows are kept open and the people spend more of their time in the open air; and, secondly, there is the fact that vaccination is not so generally practiced among this class.

EXCITING CAUSE: THE ORGANISM.—Early studies sought to find the exciting cause of variola among the bacteria, but inasmuch as it was subsequently shown that the contents of the vesicle and the vaccinal lymph when deprived of their bacteria still retained their specific characteristics, this theory could not be upheld. Later investigations demonstrated the cause of variola to be an animal organism. Van der Loeff, and Pfeiffer, independently and almost simultaneously, in 1887, described the parasites, rhizopoda and sporozoa, which they found in the vaccinal lymph and in the contents of the variolous pustules, and to which they assigned an important rôle in the etiology of vaccinia and variola. But Guarnieri, in 1892, was the first to advance a definite protozoan theory in relation to vaccinal variolous infection. He demonstrated that the two diseases owed their specific character to the endocellular action of minute protozoa which he designated respectively, *Cytorrhyctes variolæ* and *Cytorrhyctes vacciniæ*. Other investigators thereupon demonstrated that the parasite in certain stages assumed ultramicroscopical proportions, and further studies were then directed to establishing the morphology and structure of the organism. In 1904, Councilman and his associates demonstrated that these vaccine bodies were a phase of the development of a sporozoön. They definitely regard them as the cause of the disease, resting their assumption on the fact that they are always associated with its lesions, that they develop as it develops and are found under no other conditions; and that after the lesions have reached their full development, i.e., after local immunity is established and the cells are no longer capable of affording a suitable place for development, the organisms are no longer found. They also believed that variola and vaccinia are due to the same organism, in vaccinia cytoplasmic forms alone being met with; but in the calf and in the rabbit the organism occurs with the same regularity, whether the material used is that from vaccinia or from small-pox.

Prowazek and his followers (1907-1911) describe minute organisms as the etiological agents in variola and vaccinia, which they place among a group of protozoa termed by Prowazek as *chlamydozoa*, the life history of which is as follows: (1) Numerous elements intracellular as well as extracellular, which are filterable and which are present at the beginning and end of infection; (2) intracellular initial bodies; (3) transition stages to Guarnieri bodies with central inclusions and peripheral zone and accessory bodies; (4) various stages and forms of Guarnieri bodies, some of which, with their inclusion bodies, are also found on the peripheral zones; (5) finally, degenerated Guarnieri bodies and initial intracellular bodies which again break up into innumerable elementary bodies.

More recently Hallenberger reports results which somewhat modify the findings of these observers. He points out that the difference between the extracellular and the intracellular bodies is developmental, the former increasing by simple division and the latter by budding. He terms the bodies he observed *strongyloplasma*, and places them between bacteria and protozoa, the Guarnieri bodies being reaction products of the cells. The fact that these are so numerous in the experimental lesion in the cornea of the rabbit and less frequent in the products of human pocks led him to abandon the term chlamydozoa and substitute the above-named for it.

Modes of Conveyance.—Infection of variola is carried from man to man, generally occurring through contact with the contents of the efflorescences, or the local lesions, in which the contagium resides. The virus of variola is peculiarly tenacious, so that contagion may also take place by fomites, especially through infected clothing and, according to some authorities, by aërial convection, and also through insects. Variola is contagious at all stages of development from the incubation through to the last stage, indeed, until the last evidence of crusts or "cores" has been removed from the hands and feet. In fatal cases it persists after death, thus making the most careful handling of the body a matter of supreme importance.

The secretions and excretions of the body play a subordinate rôle in the transmission of the disease. They are of importance only if infected through contact with the sores on mucous membranes or with the pustules. From tests made with the blood it seems that the blood of variola patients contains the activating agent only in the early stages of the disease—before the eruption develops.

Second attacks may occur, a few being recorded. But many of them are errors in diagnosis, for experience in hospitals—especially during epidemics—shows that all manner of diseases are liable to be sent in with a diagnosis of variola.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The incubation period of variola is generally considered to run from ten to thirteen days after a known exposure. It may be as short as five days; or it may be prolonged to the fourteenth or fifteenth day. The period of incubation is generally symptomless.

Mode of Onset.—The transition to the actual invasion of the disease is apt to be sudden, the symptoms consisting of headache, severe backache, fever, chilliness, stupor and delirium, with evidence of marked toxemia. The initial symptoms, however, may be very slight, and are then apt to be followed by a mild form of the disease, but it cannot be said that severe initial symptoms necessarily indicate a subsequent severe course of the disease.

The onset is generally so acute that the patient is at once prostrated and unable to be out of bed. The temperature, whether or not preceded by a chill, mounts rapidly to 103.1°-104° F. (39.5°-40° C.), and on the second or third day reaches a maximum of 104.9°-105.8° F. (40.5°-41° C.) and even 107.6° F. (42° C.). This rapid rise in temperature is often seen also in varioloid, while in the more severe forms of variola lower temperatures are sometimes noted. The pulse, ranging between 108 and 120, is generally of good quality, except in the very severe cases, where it is apt to be thin and irregular. Respiration corresponds to the temperature. Dyspnea sometimes sets in, although neither the lungs nor the heart are affected. The skin usually is dry, the face is red, and the conjunctiva injected. The tongue is coated, dry, and sometimes serrated at the edges. There is generally a characteristic buccal fetor. Pharyngitis, rhinitis and slight bronchitis are often present. The patient complains of nausea, and there may be vomiting, especially in children. The nausea in the fulminating cases is generally persistent and accompanied by singultus and epigastric pains. The headache is usually localized in the frontal region, but it may be diffused over the entire head. Insomnia is almost complete during the initial stage, while vertigo and tinnitus are not uncommon. In children convulsions are often noted. But the most obtrusive symptom is backache, which often is already manifest during the incubation period, persisting through the initial stages up to the breaking out of the eruption. The pain is usually located in the lumbar region and is peculiarly severe and "sickening" in character; in some cases it is associated with drawing pains in the legs together with a loss of power, and joint pains suggestive of articular rheumatism and septic disease. Often stiffness and pain in the nape of the neck together with the severe headache raise the suspicion of meningitis. The heart and the lungs are nearly always negative. But the liver may be tender to pressure, though not enlarged. Enlargement of the spleen is generally marked, even in the early stages of the disease. In fact, some authorities find that the splenic enlargement is most pronounced in the early stage of variola vera, while in varioloid palpable enlargement is wanting. The condition of the splenic area, therefore, might be of diagnostic value. The bowels are constipated. The urine is of high specific gravity and is reduced in quantity. Albuminuria (febrile type) may be present; pronounced albuminuria represents an unfavorable sign, since it is generally associated with the type of the disease which develops into the hemorrhagic form. In the female menstrual-like bleeding begins at once, and although this phenomenon is often associated with other febrile conditions, it is particularly characteristic of variola.

Symptoms during Progress of Disease.—A prodromal rash appears on the first or second day after the onset of symptoms and disappears in a few hours. It may be scarlatiniform or morbilliform, either of which may be associated with petechiæ. The distribution may be general, but as a rule it involves only the lower abdominal areas, the inner aspects of the thighs, the lateral thoracic region, the axilla, and sometimes the knees and elbows. This feature occurs more often during some epidemics than others, but is generally considered to be present in from ten to sixteen per cent. of cases. Between the third and fifth day—usually in sixty hours—the actual variola eruption breaks out, the severe initial symptoms begin to abate, and the patient feels so much better that he is liable to think that he is at the end of his trouble.

The eruption appears first on the exposed surfaces of the body, i.e., those subject to the greatest irritation—the forehead, the back of the hands, front of the wrists—and within the next twenty-four hours on the face, neck, feet and trunk, in the order mentioned. It also attacks the mucous membranes of the pharynx, palate mouth and tongue, sometimes appearing in this location before the papules are seen on the skin. It may also early attack the larynx, trachea and large bronchi. A lesion that develops on the mucous membranes appears first as a red macule which soon turns grayish and is surrounded by a red zone due to the formation of a vesicle which soon ruptures. When only a few lesions are present on the mucosa discrete erosions result, but when the lesions are more numerous, more or less deep and irregular ulceration may ensue, simulating diphtheria.

The evolution of the typical eruption of variola is unique, its peculiar interest resting on the regularity with which it passes from one stage to another at certain definite intervals, such as is not seen in any other acute exanthem.

The eruption appears about the third day of the disease as small red *macules*, which in a few hours develop into *papules* about the size of a small pea, generally hard and shotty to the touch. On the fourth or fifth day (second day of the eruption) the papules develop a conical point, the beginning of vesiculation; during the next three days the *vesicle* gradually fills, increases in size until it is circular, tense and umbilicated, owing to the development of a central depression. It reaches maturity on the eighth or ninth day (sixth or seventh of the eruption). The cellular contents now become turbid, owing to the commingling of pus bodies, the umbilication disappears and the lesion again becomes rounded or dome-shaped. Careful examination after pricking of the lesions at this time will show that they are multilocular, since they fail to collapse. On the ninth day (seventh of the eruption) the typical variola *pustule* is seen. A red areola develops around the base of the pustule, the confluence of which, when the eruption is profuse and thickly disseminated, leads to a typical edema of the face, especially around the eyelids, nostrils, lips and mouth. It is at this stage that the characteristic secondary rise of temperature sets in, and at which the suffering of the patient is most intense.

In the favorable cases this fever lasts only a day or so, and on the tenth or eleventh day of the disease (eighth or ninth of the eruption) the pustules begin to dry up and the temperature falls, reaching the normal at the end of the second or the beginning of the third week. The *desiccation* process begins on the face and proceeds in the same order in which the eruption appeared. By the fourteenth or fifteenth day of the disease desquamation will be well advanced on the face. The eruption may be present in its different stages in various parts of the body, but the different stages are never seen side by side on the same part of the body. In other words, unlike the varicella eruption, that of variola does not appear in crops, though it may resemble varicella in that some of the lesions may abort at the vesicular stage.

During the desiccating stage the skin around the lesions, especially on the limbs, may become inflamed, and large, flat pemphigus-like bullæ develop. These are filled with a thin yellowish fluid, and as they rupture leave an ulcerous surface on which crusts form. At this stage the temperature may again arise, attended by more or less marked constitutional symptoms. According to the severity of the eruption and the number of lesions this secondary fever may be slight and evanescent, or it may reach a maximum of 102°-103° F. (38.9°-39.5° C.) or more, the height of the fever apparently depending upon the tension in the lesions and the extreme discomfort and irritation they cause, and to some degree also, upon the septic absorption of their contents. The fever continues even after some of the pustules rupture, and persists into the early stages of desiccation.

With the process of desiccation the subcutaneous edema subsides, the suffering is relieved, and although the patient is weak and exhausted, convalescence sets in. The process of encrustation is generally completed in about sixteen days from the onset of the illness, when the crusts begin to fall off. The crusts show a tendency to persist longest on the hands and feet, where small "cores" may remain which often have to be removed with a knife or scissors. These cores are hard, dark brown, or black masses buried beneath the skin, and on puncture evacuate a slimy substance which is readily removed with a needle. During the crusting stage the most annoying symptom is intense itching, and often, unless prevented, the patient will scratch so forcibly as to induce secondary infection. The scratching, however, does not, as is generally supposed, influence the resulting scar. Whether or not the skin scars remain after desquamation is completed, depends upon the character of the suppurative process. If superficial, the pustule dries without leaving a mark, but if the papillary layer has been included in the suppurative process, a scar will remain at its site, due to the replacement of the epithelium by vascular granulation tissue which is transformed into connective scar tissue, leaving the typical pock mark, which often persists during life. In some patients the hair falls out during the crusting stage and even later, but generally grows again, except, of course, where the hair follicles have been destroyed by the suppurative process.

In uncomplicated cases of variola vera complete recovery takes place in from three to six weeks. In the complicated cases, of course, the time is indefinite.

The blood-picture in variola during the incubation period shows marked leukocytosis with polymorphonuclears predominating; later on, in the papular stage, the leukocytes are not increased, and may even be subnormal in number. In the vesicular stage and continuing for several weeks thereafter, leukocytosis is again more or less marked with lymphocyte cells predominating; a very high leukocytosis indicates the presence of some complication. In severe cases myelocytes and normoblasts are present and if found in large numbers are considered unfavorable signs. In vaccinia the blood-count, according to Schatzmann, is analogous to that of variola, the difference being one of degree only, thus indicating the identity of the two diseases. Erlenmeyer, on the other hand, did not observe the predominance of lymphocytes in vaccinia. He believes the eruptive stage in vaccinia corresponds to the prodromal stages of variola, or that perhaps, owing to the peculiar mode of infection, the skin and the general reaction appear simultaneously.

Diagnosis.—The diagnosis of variola is neither easy nor certain before the typical eruption appears; at the same time it may be said that there is perhaps no disease in which early definite diagnosis is of such primary importance. The general symptom-complex—more or less sudden onset, headache, generalized pains, usually more marked in the lumbar region, nausea, vomiting, fever, with or without a previous chill, delirium, especially in children—is not peculiar to variola only; the addition of a prodromal rash, especially in the absence of a known exposure to variola, still more confuses the diagnosis. In the initial stage the symptoms may suggest *influenza* or *lumbago,* although the latter is rarely accompanied by headache, fever or general prostration; so that it should be easily ruled out. Influenza is not so easily excluded, especially, as may well happen, if both it and variola are epidemic at the same time. Differentiation would then be almost impossible until the actual variola eruption had appeared. If this is not seen on the fourth day a diagnosis of influenza may be safely made. Furthermore, a slow pulse compared with the temperature is also significant of influenza.

The onset of variola may also sometimes simulate *pneumonia,* and, in a certain percentage of cases, stiffness of the neck and delirium may suggest *meningitis.* For pneumonia the character of the expectoration is decisive, while for meningitis, lumbar puncture and the ophthalmoscopic picture should make the situation clear.

Differentiation between *typhus,* as well as *typhoid fever,* may sometimes have to be made. Typhus often during the first three days presents severe backache, and on the fourth day a roseola exanthem resembling the prodromal variola rash. The temperature chart in such cases should remove any doubt, for none of the acute exanthemata presents the characteristic fall of temperature as that seen at the beginning of a variolous eruption. The temperature chart is also a guide in diagnosing typhoid fever, the rise being gradual, while the onset of symptoms, unlike those of variola, is slow and insidious.

The prodromal rash that appears in a small percentage of cases may be scarlatiniform or morbilliform in character. It is comforting to know that the prodromal variolous rash does not appear in children under ten years of age (Ker). In addition, pronounced throat and tongue symptoms together with circumoral pallor are typical of *scarlet fever,* while in variola there are neither throat nor tongue symptoms, the face is more uniformly flushed, the rash is less diffuse and not so distinctly punctate. In *hemorrhagic small-pox,* however, the rash may sometimes be mistaken for those cases of severe scarlatina which present petechial spots and a very vivid rash. It is obvious that in such instances careful isolation of the patient, until the appearance of signs pathognomonic of one or the other disease, is most essential.

The morbilliform prodromal rash of variola can be distinguished from *measles* by the presence of Koplik's spots, but (as Ricketts points out) not by their absence, for the spots may have disappeared by the time the rash becomes evident. On the other hand, the lesions of variola that develop on the mucous membrane of the mouth are apt to be present early, before the papules appear on the skin, and there might be danger of confusing these with Koplik's spots. The former, however, are found chiefly on the palate and the fauces and only to a slight degree, if at all, on the sides of the mouth. It should also be remembered that an erythematous eruption is probably not due to measles unless it is associated with pronounced symptoms of coryza. Furthermore, the onset of measles is not sudden, and is not apt to be accompanied by vomiting, headache, backache and chills.

In doubtful cases the blood-picture may be of value in arriving at a diagnosis. Increased leukocytes with lymphocytes predominating and the absence of eosinophils characterizes the blood in variola, while in scarlatina, eosinophilia is marked, and in measles there are few lymphocytes and no eosinophils during the exanthematous stage. The differentiation is important, inasmuch as in case of death, a certificate of death from measles or scarlet fever, when the actual cause was small-pox, would be apt to lead to serious consequences.

In the papular stage also, variola is liable to be confused with measles, especially as the papules in the latter may be hard and shotty to the touch, like those of variola; while the variola lesions, especially in the modified form of the disease as we see it to-day, may be rather soft, particularly those of only a few hours' growth. The distribution of the eruption in such cases is probably the most reliable guide. The eruption of measles covers the entire body, while in variola the flanks are generally spared, and a papular rash on the face will generally be accompanied by a simultaneous, definite, vesicular eruption on the palate.

Differential diagnosis during the vesicular and suppurative periods in a typical case of variola vera presents little difficulty. But to-day, when the general type of variola is so mild or atypical or so much modified by the more or less general practice of vaccination, the distinction between it and other exanthemata is sometimes exceedingly difficult. This is especially true of *varicella,* which is probably the one disease that more than any other is confused with variola. In the greater number of cases the resemblance is only a superficial one, but frequently the differentiation must be made on more or less delicate indications, indeed, is often impossible even by the most expert diagnostician.

The age of the patient is not significant, for varicella does sometimes occur among adults (p. 223), although variola, owing to early vaccination, is rare among children. The initial symptoms may be a guide, since in varicella the eruption, as a rule, is the first sign of the disease, which is not the case in variola, and generally appears at the same time with the constitutional symptoms, particularly in children. But in the adult the prodromal stage is often long and severe and presents all the symptoms of variola. It is these cases that enhance the difficulties of differential diagnosis. In varicella the eruption preferably attacks, first, the covered portions of the body, while in variola the eruption appears first on the face and exposed portions, the greater number of lesions appearing on the face, the forearms, and the wrists; on the legs and thighs, if the eruption is profuse, while the abdomen is usually least affected. This is considered by Ricketts one of the most important distinctions between the two diseases. The presence of numerous lesions on the palms and soles would, in his opinion, argue against chicken-pox and in favor of small-pox.

As to the character of the eruption itself: first of all, the variola eruption does not come out in crops, as does that of varicella; secondly, the development of the varicella eruption often is so rapid and so symptomless that it seems to miss the papular stage and is recognized only in the vesicular stage; finally, the shape of the lesions is characteristic. Those of varicella are oval, often irregular and soft and velvety to the touch, while the variolous lesions are round, almost invariably so, and are hard and shotty.

Both diseases may, of course, develop anomalies with regard to all these points, but it is more unusual for varicella to mimic variola than it is for a variolous eruption to imitate varicella, which, of course, is fraught with greater danger.

The distribution of the eruption in such instances again is a valuable guide. Indeed, according to Ricketts, it is finally the distinguishing feature on which the greatest reliance can be placed. This is true even in the cases which present the greatest difficulty, i.e., those in which the eruption is scant, although here the character of the lesions may possibly be a more valuable guide.

The differentiation of the two diseases is of such importance that we find it expedient to use Ricketts' tabular form in summarizing the main differences between the eruption of variola and varicella:

VARIOLA	VARICELLA
1. The rash is most abundant on the face; most scanty on the abdomen and chest.	1. The abdomen and chest are covered as thickly as the face, or more thickly.
2. The rash is much more abundant on the back than on the abdomen.	2. The abdomen is covered equally with the back.
3. The rash is more abundant on the shoulders than across the loins, and on the chest than on the abdomen.	3. The distribution is indifferent.
4. The rash favors the limbs and, generally, the arms, next to the face.	4. The rash tends to avoid the limbs.

VARIOLA	VARICELLA
5. The distribution on the limbs is centrifugal.	5. The distribution on the limbs is centripetal.
6. The rash favors prominences, and surfaces exposed to irritation; it tends to avoid protected surfaces, flexures and depressions.	6. The rash behaves indifferently.
7. The lesions are deep-seated, and have an infiltrated base.	7. The lesions are superficial and the base is not infiltrated.
8. The lesions are generally circular in outline.	8. The lesions frequently have an irregular outline; when they lie near a flexure they are apt to be oval or elongated.
9. The lesions are homogeneous in character; or if they are heterogeneous they are heterogeneous by law.	9. The lesions often are not homogeneous; and the want of homogeneity bears no relation to the sizes of the lesions and to their situation.
10. The vesicles, generally, are multilocular.	10. The vesicles, generally, are unilocular.
11. Frequently some of the vesicles are indented.	11. The vesicles are never indented and seldom dimpled.

Among other pustulous eruptions which may resemble variola may be mentioned *syphilitic eruptions, acne, impetigo contagiosa,* and the *pustulous exanthemata of septic diseases.* The Wassermann reaction and the history of the case should exclude syphilis, while in acne and impetigo the absence of initial symptoms preceding the outbreak of the eruption should serve to make the proper diagnosis. In addition to this, the vesicles of impetigo are unilocular, and the redness surrounding the sore is not so marked as in variola. *Rashes due to digestive disturbances or to drugs,* bromids, iodids, etc., can be recognized by the absence of initial symptoms and the history of dietary indiscretion, or the administration of certain drugs.

In *pneumococcic septicemia after pneumonia,* much confusion may be caused by the presence of a pustulous eruption on the back, the chest and the extremities, but the distribution of the sores and the absence of a history of exposure to variola should prevent an error of diagnosis in such instances.

The vaccination test on the cornea of the rabbit is often resorted to in suspected cases. Inoculating the contents of a variola pustule into the rabbit's cornea produces a typical lesion in about thirty hours, at first a thickening of the epithelium, which in a day or two develops into a sore, stained sections of which present Guarnieri bodies.

The final test, however, is convincing evidence of vaccination. Successful vaccination within half a dozen years, at least, or revaccination at any time, or a successful vaccination during the early stages of the disease—especially after the third day of the eruption—may be taken to indicate that the ailment is not small-pox.

Complications.—The complications of variola are generally related to the severity of the skin lesions, especially during the suppurative stage, and are due to pyogenic infection of the skin, the eyes and the mucous membranes of the nose, mouth, the throat and the respiratory tract.

The presence of a *pustule on the eye* may lead not only to severe conjunctivitis, but also to ulceration of the cornea followed by opacity, perforation and even panophthalmia. Severe cases may lead to permanent blindness.

More or less serious *ear trouble* may also complicate variola. The external canal as well as the tympanum and the mucosa of the eustachian tube sometimes become congested and swollen, and purulent otitis media and even mastoiditis or other sequelæ of otitis media may occur.

The *eruption on the mucous membrane of the nasopharynx* may lead to phlegmonous inflammation of the esophagus, tongue and fauces, the latter sometimes suggesting diphtheria, or it may lead to an ulcerative condition of the larynx with its attendant sequelæ; there is nearly always some hoarseness, although complete loss of voice is rare. When it does occur it is a bad prognostic sign. Edema of the glottis also often complicates variola, and may be severe enough to demand tracheotomy.

The *damaged condition of the skin* may lead to bed-sores, superficial abscesses and boils, unless great care is taken to prevent them; while cellulitis, erysipelas and tetanus may appear during the stage of encrustation and result in death.

The *most important complications of variola*, however, are those that involve the *respiratory passages.* Bronchitis is decidedly not uncommon and may be serious and develop into bronchopneumonia. Lobar pneumonia and pleurisy often accompany variola; while heart affections—pericarditis (serofibrinous or purulent) and myocarditis—are sometimes met with. Adenitis, cervical and axillary, and orchitis (in the male) also frequently complicate variola. The latter is by some authorities regarded as part of the symptom-complex of the disease, but others feel justified in considering it a complication, since changes have been observed postmortem that suggest that the orchitis develops during the evolution of the eruption. Small, hard nodules may sometimes be palpated (*intra vitam*) during the pustular stage.

Nephritis is not unusual. *Paralysis* is sometimes reported. It is, however, usually transitory and disappears in a few weeks. It is generally interpreted as a peripheral neuritis, but (as McClure points out) is more likely the result of the effect of the toxin on the spinal cord and the meninges. Cases of *paraplegia* and *hemiplegia* are also recorded, but are very unusual.

Clinical Varieties.—The clinical course of variola is determined by the severity and the character of the eruption, the disease accordingly presenting several clinical varieties, the most malignant of which is *variola hemorrhagica,* occurring in two forms: variola hemorrhagica purpura (black small-pox) and variola hemorrhagica pustulosa. Less malignant is the type known as *variola vera* in which the lesions may be confluent, semiconfluent or discrete, the latter gradually merging into the third variety, known as *varioloid,* a modified form which, in some instances, is so aberrant as to omit the eruption altogether, being then known as *variola sine exanthem.*

Before vaccination was as commonly practiced as it is to-day among intelligent and civilized people, the hemorrhagic type and the malignant forms of variola vera were much more frequent than they now are and were more prevalent in some epidemics than in others.

VARIOLA HEMORRHAGICA.—The hemorrhagic forms of variola seem preferably to attack young people and pregnant women. The latter, if they survive long enough, usually abort. The two forms are manifestations of different degrees of the severe toxemia—in *purpura* the hemorrhage into the pocks from the mucous membrane occurs during the eruptive stage, while in *pustulosa* it takes place during the vesicular or pustular stage. The initial symptoms in either are severe.

Variola Hemorrhagica Purpura.—On the evening of the second day, or on the third day, in the purpuric form, a diffuse hyperemic rash appears on the body, developing especially in the groins, starting with small punctiform hemorrhages which gradually increase in size; at the same time the conjunctivæ are more or less ecchymotic and there may be hemorrhage from the mucous membranes. The skin assumes a purplish or even a plum-colored hue, and the edema of the face, together with large conjunctival hemorrhage, and sunken appearance of the cornea, gives the patient a truly ghastly aspect. Death generally results in three or four days, but may set in even before the rash appears.

Variola Hemorrhagica Pustulosa.—The clinical picture of *variola hemorrhagica pustulosa* is not much more encouraging. The fatal course may be delayed to the seventh, eighth or ninth day, but is generally run in three to four days. The earlier the hemorrhage takes place the greater is the danger. When the lesions succeed in progressing to the pustular stage, hemorrhage may occur between the lesions or at their bases, the prognosis being a little more favorable when the latter is the case.

VARIOLA VERA.—*Confluent Types.*—In the confluent types, as their name indicates, the lesions are more or less closely sown so as to adhere or to merge one into another during the pustular stage. This refers particularly to the eruption on the face and the exposed surfaces; on the body itself the pocks are, as a rule, discrete. The evolution of the eruption is generally rapid, with a very rapid dissemination over the body, especially marked on the face, which becomes edematous and distorted.

Involvement of the mucous membranes leads to complications which in turn unfavorably affect the temperature. The condition progresses from bad to worse and the end generally comes with associated symptoms of general sepsis.

When recovery takes place convalescence is slow and protracted.

Desiccation of the confluent lesions is retarded, owing to the reformation of suppuration in the very diffuse eruption. The normal process is also interrupted by the development of abscesses and furuncles. After the primary desquamation thin crusts often form again and again before the final healing of the lesions takes place. The lesions on the mucous membranes also heal very slowly; and fever, owing to complications, is apt to persist into the third week of the disease.

Discrete Form.—In the discrete form of variola vera the lesions are fewer in number and the disease is not so apt to be fatal, its malignancy depending upon the number of lesions and the presence or absence of complications. The skin presents the same inflammatory edema, but, as the pustular stage is reached, the temperature falls, the general condition improves, and in uncomplicated cases convalescence sets in toward the end of the second week.

VARIOLOID.—The benign variety of variola, known as varioloid, is by some authors made to include all mild or aberrant forms of the disease, while others restrict the term to those cases that have been modified by vaccination.

Varioloid differs from variola vera in running a shorter and more benign course after the eruption once appears. The incubation period is the same, but the period of invasion may be longer or shorter than in variola vera, while the symptoms may or may not be severe, and in no way indicate the clinical type that the disease will assume. The latter can sometimes be foretold by the prodromal rash which in variola vera is generally petechial, while in varioloid it is more likely to be erythematous or morbilliform. It is the character of the eruption, as we have seen, that finally determines the history of the disease itself. In varioloid the temperature, if it has been high, falls rapidly during the eruptive period, reaching the normal on about the fourth day, without any secondary rise at the suppurative stage, except in very rare instances. The eruption may vary both in the order and extent of distribution and in its evolution. Instead of regularly beginning on the face or exposed surfaces it often appears first on the trunk or simultaneously in different parts of the body. The number of efflorescences may vary from a very few discrete pocks to a profuse eruption diffusely spread over the skin surfaces. The single pocks, beginning as red macules, are quickly transformed into papules, many aborting at this stage. Others go on to vesiculation and abort at the beginning of the pustular stage, and some very rapidly go through the pustular stage—a fact that often adds to the difficulties of diagnosis. The vesicle begins to fill about twelve hours after the macule appears, and on the third day (of the eruption) shows signs of suppuration which nearly always is superficial. The areola surrounding the pustule is small without any evidence of inflammatory or edematous swelling. Desiccation begins on the fifth to the seventh day (of the eruption); or earlier in the abortive efflorescences. The pustules simply dry up without rupturing, and leave a thin brownish crust which, being superficial, falls off easily. It is only in the buried crusts on the palms and soles that desquamation is apt to be slow. Slight prominences and pigmentation which remain after desquamation disappear in a few weeks without leaving any trace of the disease.

The mucous membranes are often affected but not so severely. The visible pocks are few in number, and although catarrhal inflammation of the buccal mucosa, dysphagia, hoarseness and coryza are present, they are not so annoying as in variola vera, and never give rise to serious ulcerative and necrotic processes. This type of the disease is probably not so infectious and contagious as variola vera, since it practically never attacks an individual who has been successfully vaccinated, even at a remote period.

Variola sine Exanthem.—Some exceedingly mild forms of varioloid, in which only a few pocks develop, form the transition type to variola sine exanthem, in which there is no sign of the eruption on the skin or on the mucous membranes. The etiology of the disorder rests altogether on circumstantial evidence. Often a person with somewhat defective immunity, possibly from a very remote vaccination, who is known to have been exposed to small-pox contagion, develops symptoms so typical of the invasion period that the eruption is naturally expected to appear on the third day, but fails to do so. Instances of this kind have been observed during certain epidemics in sufficient numbers to warrant the inclusion of the form as a variety of varioloid. Marked backache in these cases should arouse the suspicion, while the appearance of a prodromal rash should establish a diagnosis of variola sine exanthem; for often the disease is not recognized except in its effects, such cases having been known to form the source of infection in a case of variola vera.

Treatment.—Prophylaxis.—Prophylaxis against variola is comprised in the one word—**vaccination.** With this definite preventive measure at the command of medicine for more than a century, the beneficial value of which is beyond estimation, the subject of variola should today be a matter of historical interest only. Unfortunately, however, the light has not yet penetrated into certain quarters and cases of variola do occur among unvaccinated individuals or among such persons who have to some extent lost the immunity acquired by a remote vaccination.

The question of the *persistence of the immunizing effects of vaccination* is an important one. There is no doubt that it establishes life-long immunity to a certain degree, but some persons show a greater predisposition to the disease than others, and at a more or less remote period the protective value of vaccination begins to diminish. The thirtieth year of life is generally regarded as the period at which this becomes evident—a fact that has been recently confirmed through the opportunities afforded for the study of this question during the world war. It appears that "cradle" vaccination and revaccination at puberty are effective in the vast majority (about 95 per cent.) of individuals up to about the fourth decade, the effects beginning to decline after the thirtieth year, so that revaccination of all persons between the thirtieth and fortieth years is advisable. Among 1,000 (500 males, 500 females) individuals, Gins obtained 30.4 per cent. successful revaccinations among those between thirty-one and thirty-five years, 62.7 per cent. among those between thirty-six and forty years of age, and about 65 per cent. among those beyond the fortieth year. A decided increase is also seen in the severity of the disease (in vaccinated persons) acquired after the thirtieth year as compared to that acquired before that period. Among 58 cases that contracted variola between the ages of fifteen and thirty years, 60 per cent. developed mild cases, 36 per cent. moderate, and 16 per cent. severe cases, with only one death in the series. Among a group of 328 individuals over thirty years of age who fell ill, 68 per cent. were beyond the fortieth year; of these, 33 per cent. developed mild, 43 per cent. moderate, and 24 per cent. severe cases, with a death rate of about 13 per cent. For the years between thirty-one and forty, the cases were mild in 52 per cent., moderate in 29 per cent. and severe in 16 per cent., with a death rate of 4 per cent.

Second only to the prevention of small-pox by vaccination and revaccination is the importance of **preventing its spread.** Notification to the public health authorities and **isolation** of the patient are the first steps to be considered. Wherever possible, prompt removal of the patient to an isolation hospital is demanded. The hospital, whenever feasible, should be situated in a sparsely settled district, since the disease is carried by the air and by insects, and small-pox hospitals have often been suspected of forming the foci for the spread of the disease. After the patient has been thus placed in strict quarantine, vaccination of all contacts and suspects should be rigidly enforced, since variola is highly infectious from the moment of the appearance of the initial symptoms. The patient's whereabouts during the two weeks (incubation period) prior to his illness should be investigated, in order to discover any possible unreported contacts. Successful vaccination or revaccination of these persons, if done within three days of exposure, will usually prevent any secondary outbreak, and if done as late as the sixth day, will certainly modify the course of the attack. Contacts who fail to present evidence of recent successful vaccination should be kept in quarantine for fourteen days, or until all danger of developing the disease has passed. Those, however, who show satisfactory vaccination marks of comparatively recent date should be kept under observation, but may be allowed their liberty; for it is as sure as anything in medicine that they will not contract the disease. The economic loss and great inconvenience attendant upon maintaining a strict quarantine should be taken into consideration by the health authorities and the physician, and should not be imposed upon those whom experience has shown to be practically immune to variola.

The patient's **home should be fumigated,** and the furnishings of the room and the room itself **cleansed with soap and water,** and **renovated,** if possible. This renovation is more essential in cases of small-pox than perhaps in any other acute infection, owing to the extreme tenacity of the virus of the disease.

The patient should be kept under **strict quarantine** until all the crusts have separated, especially those (buried cores) on the palms and soles. When very persistent, the desquamation process can sometimes be hastened by means of **warm soap and water baths.**

Only such persons should be employed to attend a small-pox patient who have been properly protected by vaccination or by revaccination before entering the sick-room. In reality it is good practice routinely to **vaccinate any one who is assigned to attend the patient.** The nurse should **disinfect** everything that comes in contact with the patient, such as bed and body linens, eating utensils and dishes. Bandages and dressings should be burned, and the excreta disinfected before being carried from the room. General rules, as given in the chapter on Scarlet Fever (pp. 257-258), should be observed in hospital cases as well as in those treated in the home.

The strictness of quarantine should in no way be relaxed in a case of *varioloid.* The latter condition may be as infectious as variola vera, and may give rise to any of the more severe and fatal forms.

Varioloid and the milder forms that are generally met with to-day need very little treatment. Isolation provides the necessary rest which is about the only thing the patient will require after the initial fever has subsided.

GENERAL TREATMENT.—The general treatment of variola is purely **symptomatic.** The patient should be made as comfortable as possible. Plenty of **fresh air, a comfortable bed,** with light bed-coverings supported by a frame or cradle, and frequent change of sheets are essential. A **water-bed** often proves serviceable in relieving the discomfort of the numerous hard lesions.

In the *preëruptive stage,* or the period of initial fever, the severe headache can be relieved by **phenacetin,** or **caffein,** cautiously given; and for the backache, **aspirin combined with codein** is useful; joint pains should be treated with **hot fomentations or poultices; dry cupping** has also given satisfaction. Thirst should be relieved by copious draughts of **water** with or without the addition of **lemon juice** or in the form of the Imperial Drink (p. 267). For the chilliness the use of **hot water-bags or bottles** is indicated. For the fever at this stage **cold sponges or cold packs,** according to the degree of fever and the presence or absence of nervous symptoms, will be found efficacious.

Diet during the febrile stage should be limited to liquid nourishment, milk, buttermilk, albumen, water, etc. After the initial fever subsides advantage should be taken of the afebrile period to push the diet to include as much nourishing solid food as the patient will take, such as steak, chops, eggs, milk and the more easily digested vegetables. Thus fortified, the patient will be better able to combat the severe struggle that is in store for him during the stage of suppuration. During the secondary fever the diet is again limited to the customary febrile régime. Sometimes, owing to the presence of the specific lesions in the mouth and throat, there will be difficulty in swallowing and the diet will have to be limited to liquids throughout the illness. It is important for the patient to have as much nourishment as possible. Feeding should be regular at two or three-hour intervals, including the night, if the patient is awake. We would suggest milk—either plain or peptonized, with the addition of thin gruel, or in the form of milk punch—eggs, eggnog, broths or beef juice, four to ten ounces pressed from fresh cut beef, and if desired, mixed with milk. Where there is difficulty in swallowing, the liquids are better given cold; rectal feeding may have to be resorted to in severe cases, although it is not apt to be successful, possibly on account of the presence of lesions in the rectum.

Orthoform, one grain (.065 gram), given just before feeding, may be helpful; failing this, the throat may be painted with a 1 per cent. solution of **cocain hydrochlorate,** which usually will remove the difficulty of swallowing. **Alcohol** is well borne by small-pox patients, and in the severe cases may be given in the form of brandy or whiskey, in milk, or in a small amount of glycerin or syrup and water to avoid irritating the throat; in the mild cases alcohol is not usually indicated.

During convalescence the régime should again be liberal and the appetite stimulated, if necessary, by **tonics** containing strychnia and alcohol.

For the *secondary fever in its early stages* **cold baths** in the form of **packs and sponging** will prove of value; but during the *later or suppurative stage* **warmth** is indicated. This is usually given in the form of the **continuous warm bath** for several days at a time, with the patient placed in a sort of cradle in the tub, the water to be kept at a constant temperature of 95° F. (35° C.) It is important not to allow the water to cool, as a lower temperature may cause the patient to become depressed. Ruhräh considers this one of the best means of treatment at our disposal. It lessens delirium, should it be present, keeps the skin clean and oftentimes lessens absorption and prevents the formation of scabs and of suppuration beneath the scabs.

Delirium is treated in the usual manner by the use of **sedatives**—bromids, with or without chloral or morphin. The administration of a **cathartic** oftentimes assists in quieting the patient. The delirium may be severe and may necessitate **restraint,** but this should be resorted to only when absolutely necessary, in order to avoid possible rupture of the pustules and injury to the severely traumatized skin by tugging and pulling at the restraining bands.

For *insomnia,* **hypnotics,** such as veronal or trional, may be of use. Or sometimes one or two large doses of **whiskey** may bring the desired sleep.

There are few, if any drugs, that abort or alter the attack in every instance. Some authorities, Ker, for example, find **salol,** 10 grains (0.65 gram) useful if given every four hours as soon as the eruption appears. In some instances this has brought about a more rapid evolution of the eruption to the stage of pustulation, the latter being incompletely developed. This writer makes the reservation, however, that nearly all cases so treated had been vaccinated in infancy and therefore have retained a certain degree of protection. The drug is sufficiently harmless to be worth a trial.

In line with the modern use of colloidal metals in the treatment of infections, gold has proven useful in some instances. Septêt and Manet used intravenous injections of **colloidal gold** in five cases of variola confluens and succeeded in obtaining a reduction of the fever during the suppurative stage which, in spite of the serious condition, never rose above 104° F. (40° C.). In one case suppuration was altogether prevented, while in another (secondary hemorrhagic variola) the cutaneous symptoms were rapidly controlled and crusting encouraged. Complications during convalescence were limited to abscess formation (two) in one instance, and in another to abscess and adenitis; while in the cases not treated with the gold, convalescence was interrupted by severe furunculosis, multiple abscesses (19 in one case), diffuse phlegmon, erysipelas, etc. No visceral disturbances followed the injections which were given, one dose daily of ½ c.c. and 1 c.c. respectively, on two successive days, followed on the fourth day by 2 c.c. of the colloidal gold, the latter being the largest amount that was given. The administration was stopped as soon as the temperature fell to 100.4° F. (38° C.). Each injection was immediately followed by an injection of **camphorated oil,** for the purpose of obviating cardiae symptoms during the reaction.

Owing to the swollen condition of the tissues it may sometimes be difficult to give the injections; in two cases in this series it would have been altogether impossible to do so had the patients not been treated before the eruption broke out.

Treatment of the eruptions is directed toward keeping the lesions clean and intact. Welch and Schamberg recommend painting the confluent parts with a freshly prepared **tincture of iodin,** pure, or, if desirable, diluted, repeated daily or every other day. This we find secures early separation of the scabs, reduces the tendency to abscess formation and lessens the inflammation of the skin in the later stages. Others apply a solution of 25 per cent. **alcohol with boric acid**; and still others advise spraying with **alcohol alone or combined with some other antiseptic solution,** or with **ether and bichlorid,** 1/3,000 or 1/5,000. During the period when the lesions begin to rupture **compresses of permanganate of potassium** frequently changed will serve to keep the skin clean and remove the discharging pus which, if allowed to dry, is apt to lead to formation of crusts and abscesses beneath them.

Ointments and dusting powders are not indicated during the early stages of the eruption, but when the crusting period sets in, a **bland ointment** will be found useful in reducing suppuration, keeping the scabs soft and hastening desquamation. **Warm soap and water baths** several times daily serve to aid in the separation of the scabs, and any of the dusting powders will relieve the irritation that results after the scabs fall off. **Alcohol and alum water,** judiciously used, will serve to harden the tender skin.

Should *erysipelas* supervene it is best treated by wet dressings. *Abscesses and boils* should be incised and drained. *Bed-sores,* or *gangrene of the skin,* should either develop, are treated in the usual manner.

One of the most aggravating symptoms at this (crusting) stage is the *violent itching.* It often causes insomnia and marked nervous symptoms, while the consequent violent scratching increases the chance of secondary infection. It can be treated by **spraying,** with alcohol with or without menthol (½-1 per cent.); or by **sponging** with carbolic acid water (1/40); or by the application of salicylic acid, or of ichthyol diluted with glycerin. Either of these may also be used in the form of ointments, not in the early stage, but later on.

Anything that prevents suppuration also favorably affects the resulting scarring. This is best accomplished by the **tincture of iodin,** already mentioned, while the softening of the scabs, which, if removed, is supposed also to reduce the scarring, is often hastened by the use of an ointment composed of **bicarbonate of soda** 2 drams (8 grams) **and petrolatum** 1 ounce (30 grams), as recommended by Welch and Schamberg. Ruhräh advocates frequent bathing in water, to which some antiseptic is added, such as **bichlorid of mercury** (1/10,000) **or alum** (1/1,000). One pound of the latter to a tub (500 liters) of water would be an approximate proportion.

The small-pox patient emits a disagreeable odor which is annoying to himself as well as to his attendants. It can be controlled by frequent bathing in water, to which **permanganate of potassium** has been added.

In former times small-pox was one of the most fruitful sources of blindness, mainly due to the omission of prophylactic care of the eyes. It is therefore important to make the toilet of the eyes part of the routine treatment of variola. *Mild conjunctivitis* will require merely **irrigation of the eyes** three to four times daily with **salt solution** or **boracic acid solution,** and anointing the lids at night with an ointment of **yellow oxid of mercury,** ½ grain to ½ ounce (30 milligrams to 15 grams). In the *severer cases* this should be supplemented with **instillations of argyrol,** 10-25 per cent., while for *very severe conjunctivitis* **cold compresses,** one hour at a time, three times daily, will be necessary.

Keratitis should be treated with **irrigations of boric acid, instillation of argyrol,** the application of the **ointment of yellow oxid of mercury** (as above), and also **atropin** in a one per cent. solution, one or two drops to be instilled three times a day. In addition to this, the more severe cases will require applications of hot compresses one hour at a time, three times daily.

Ulcers that are deep and threaten to perforate should be gently touched once a day with pure **carbolic acid** or with **tincture of iodin.** And for clearing up corneal opacities it is well to instil **dionin,** beginning with a 4 per cent., and gradually increasing to a 10 per cent., solution, two drops twice daily, and to apply gentle **massage** to the cornea with the ointment of **yellow oxid of mercury,** 1 grain-2 drams (.065 gram-8 grams).

The *throat condition* which often is annoying can be relieved by the use of **cooling drinks.** The *mouth* should be kept clean by frequent washings with any of the **bland antiseptic washes,** of which **permanganate of potash,** 1/4000, is perhaps the most efficacious, according to

Ruhräh. The *tongue and gums* can be gently swabbed with a **mixture of glycerin, boric acid and water.** If the inflammation of the tongue is severe it usually yields to painting with **glycerite of tannic acid,** but **incision** may sometimes be required. Severe *edema of the glottis* may require **tracheotomy,** which often is particularly difficult to perform on account of the large hemorrhage that is apt to ensue when the tissues of the neck are very much swollen.

For the treatment of the *unsightly and disfiguring scars* remaining after an attack of variola, Unna, Jr., finds the use of **carbon-dioxid snow** in short doses—three, five to ten seconds, according to the individual skin reaction—the most useful. The technic, however, is a delicate one and requires the services of a skin specialist. **Electrolysis** is also recommended by Unna for treating the more prominent scars, while chemical treatment with **thiosiamin and its derivative, fibrolysin,** has also been of service in his experience. The former is applied in the form of a salve, and the latter in subcutaneous injections. Their use favors resorption, as do also **plasters composed of salicylates and mercury.**

The effect of the color red in the form of hangings and curtains about the patient has been known since the early thirteenth century. Finsen, in our time, applies the method in the form of **red-light treatment.** Reports of the results are so lacking in uniformity as to raise considerable doubt in regard to its value. Finsen believes that the exclusion of the chemical action of actinic rays must necessarily diminish the severity of the inflammation and lessen the number of lesions that may develop. He places the patient in what is practically an unventilated, photographic dark-room, from which all but the red rays are excluded. Indeed, some authorities think it necessary to test the glass that is used in order to make certain that no other light enters. The mental effect on the patient confined in such a room is shown in psychic disturbances, restlessness and delirium.

Dreyer attempts to overcome this undesirable effect by excluding the actinic rays more directly by the use of dressings saturated with permanganate of potash, which gives the red coloring and at the same time acts as a disinfectant and a deodorant. He claims to have observed a decided diminution of suppuration, absence of odor and reduction both in severity and duration of the suppuration. This method presents the great advantage of permitting the use of that most valuable therapeutic agent, fresh air, and at the same time obviates the unpleasantness, both for the nurse and patient, of the depressing effect of enforced seclusion in a darkened room.

SERUM THERAPY.—Serum therapy has been suggested and tried, but has not met with success, owing mainly to the enormous amount of serum required, which according to Thomson and Brownlee, is about one-fiftieth part of the body weight for the adult and about one-twentieth for the child. These authors used the serum of immunized heifers which they found, if injected into another heifer recently vaccinated, provided a certain degree of immunity against vaccination.

The use of serum from a recovered variola patient has also been tried. Although a rational method, it has not met with success; the amount of serum obtainable is small and the results not satisfactory.

Prognosis.—Various factors determine the prognosis of variola. As mentioned in discussing the clinical varieties, much depends upon the character of the specific lesions, and it may be stated here that the danger is in direct proportion to the number of lesions on the face and hands. The fatal character of the hemorrhagic varieties has already been alluded to. In addition to this, there enter the age and condition of the patient and the efficacy of vaccination. Children are more apt to succumb than adults. During the epidemic in Montreal during 1884-1886, over 85 per cent. of deaths occurred among children under ten years of age. As already stated, pregnancy unfavorably influences the course of the disease; naturally, also, intemperate habits and debility are not without their effects. Complications—particularly pharyngitis, laryngitis and bronchitis—often are the direct cause of death. But it is the unvaccinated that supply the greatest number of fatalities in variola. In Welch's collected statistics of 5,000 cases occurring during the epidemic in Philadelphia from 1870-1874, the total death rate was 31.2 per cent.; of this number, 54.18 per cent. occurred among unvaccinated against 1.29 per cent. among vaccinated individuals. The death rate depends upon the form of the disease that prevails. In the hemorrhagic form, recovery is very rare; in the confluent form, in the unvaccinated, the mortality may be as high as 50 per cent. The type of the disease as we now see it is eminently benign, complete recovery without any permanent after-effects being the general rule.

In the severe cases of variola pitting from destruction of the skin often results to such a degree as to produce loathsome disfigurement of the face.

Blindness, as already stated, has been known to result when keratitis with sloughing has complicated the illness.

Pathology.—Councilman describes the histological changes in the skin in variola as due to degeneration of the epithelial cells and exudation into the degenerated part. Degeneration begins in the nuclei of the epithelial cells and is associated with a reticular degeneration of the cytoplasm which may affect all of the lower cells of the epidermis, the result being a characteristic multilocular pock or pustule. This development may be confined to the epidermis or it may also involve the corium which then forms the base of the pustule. The smallest visible papules are due to exudation which, together with cell degeneration, sets in early. According to Councilman, "the earliest visible lesion is really a vesicle, but the exudation enclosed in a number of small spaces does not give the swelling the macroscopic appearance of a vesicle." Leukocytes appear later in the exudate, being attracted by the necrosis. Toward the final stage of the pustule the cells in the exudate, as well as in the degenerated epithelium, break into fragmentary indefinable granular masses.

The exudate in young vesicles rarely contains red blood-corpuscles, although a few are sometimes present in the pustule. Only a few eosinophils are found in the exudate in any of the stages. Few polynuclear leukocytes are found in the blood in variola. This can hardly be explained by the paucity of these cells in the skin lesions since, in the lesions in the lungs and mucous membranes which are due to streptococcic infection, the exudate presents the usual cell character.

Bacteria are generally absent in a microscopic study of the vesicles and the pustules. Councilman, in but a few sections of the numerous ones studied, found a few cocci, usually in chains or pairs, occurring more frequently in the corium than in the epidermis. But in no instance was their relation to early epithelial degeneration such that they can be regarded as the causative factor of the disease.

The specific organisms, according to Councilman, are probably brought to the skin by the blood. They enter the epithelial cells at a single point which forms the starting point of the lesion. In purpuric small-pox the organisms reach the skin in larger numbers, so that the condition which ordinarily is found only at the primary focus of vesicle formation is extended over a larger portion of the epidermis.

Repair of the lesions sets in early. The process takes place by absorption and drying up of the fluid portion of the exudate and degeneration of the epidermis, during the course of which the "residual mass of degenerated epithelial cells, leukocytes and débris enclosed between two layers of horny epidermis, the old and the newly formed, is exfoliated."

The lesions, except those on the palms and soles, generally show umbilications, due to no one cause, but in a measure to the primary, hyaline, fibrous degeneration of the epithelial cells, the central and primary point of the lesion, which prevents distention at this point, and partly also to greater adherence of the cells at points where sweat glands and hair ducts pass through the epidermis.

The lesions on the mucous membranes develop in the same way as those of the skin, except that, owing to the absence of a horny layer, the degenerated cells are cast off, so that the specific character is seen only in its early stage, the vesicle being rarely seen and the pustule never.

In addition to the specific lesions there are other non-specific ones which, at autopsy, are frequently found on the soft palate and the uvula, consisting mainly of superficial loss of substance with deep necrosis of the underlying tissue, and containing streptococci and polynuclear leukocytes, numerous when compared to those in specific lesions.

The presence of specific lesions and erosions is often noted postmortem in the upper respiratory tract and on the tonsils, the soft palate and in the nasopharyngeal region, and extending to the larynx, the bronchi, sometimes also on the uvula and the vagina.

Bronchitis is the most common lesion associated with variola, and is usually attended with more or less extensive bronchopneumonia, affecting both the large and the small bronchi. In fact, pulmonary involvement is the most frequent and the most serious complication of variola and often is sufficiently pronounced to cause death without the aid of the specific disease itself. Different varieties of pyogenic cocci are constant findings in these cases, streptococci and pneumococci being the most frequent, in the order named.

The digestive tract is comparatively free from specific changes. A few typical efflorescences may develop on the esophagus, but the stomach and intestines are not affected, although occasionally a few pocks develop on the lower part of the rectum. The changes that are found in the gastro-intestinal tract are mainly catarrhal, or in the hemorrhagic type of variola, hemorrhagic from extravasation into the mucosa.

The heart, when death occurs at the suppurative stage, shows a lax myocardium and slight indications of fatty degeneration. Endocarditis is seen only in septic cases.

The liver is enlarged, most markedly so in the pustular and crusting stage, and postmortem shows cloudy swelling and evidence of fatty degeneration. Cloudy swelling also marks the changes in the kidney which are found in all cases of variola, and which may be seen at any stage of the disease. Glomerulonephritis is also observed and, clinically, develops during convalescence. Enlargement of the spleen is especially pronounced in cases that die early. Its capsule is tense and shiny, the consistency of the organ being much softened and its color darkened. In the later stages these changes often disappear.

The testicles also show the same disseminated foci of necrosis in the interstitial substance, in the form of dense, yellowish areas, varying in size from that of a pinhead to that of a pea. This change in the testicles is one of the very pronounced characteristics of variola in the male.

Necrotic changes were noted by Chiari also in the bone-marrow during the eruptive period; these he has designated as *myelitis variolosa.* To these changes, some authors attribute the severe lumbar pains that characterize the disease. Muir, in a later study, paid great attention to the blood and bone-marrow. He found a marked diminution or total absence of polynuclear cells—a fact which Councilman was subsequently able to confirm.

Historical Summary.—The history of variola is the history of perhaps the most constant, extensive and malignant scourge with which mankind has been afflicted. The early origin of the disease is obscure. Although Hippocrates, Galen and other ancient writers describe an eruptive disease which may be small-pox, the omission of any mention of the characteristic pock marks by these authors as well as by later Greek and Latin writers, makes it more likely that the description refers to the plague and not to small-pox.

Probably the first definite mention of variola is contained in ancient Chinese medical literature. A memorial (written from memory and found in the Royal Museum at Pekin by some missionaries) contains an account of the disorder, together with the description of the fever and the evolution of the eruption into pustules which increase, suppurate, flatten and form crusts. According to this account the disease was introduced into China during the Tcheou dynasty (1122 B. C.), and since the Ssong dynasty (590 B. C.) had been combated by the use of inoculation of the small-pox material.

The disease was also known to ancient India, the inhabitants of which are said to have worshiped a goddess, Patraglia, who presided over the small-pox.

Both among the Chinese and among the Brahmins of India the custom of variolation was practiced from earliest times, the process among the latter being entirely in the hands of the priests and attended with all kinds of religious ceremonials.

Variola is also supposed to have been prevalent from time immemorial among the Negroes of Central Africa, whence it probably spread by way of the Red Sea, and from there extended to the Arab tribes, appearing (about 569 A. D.) among Abyssinian troops who were besieging Mecca, and so depleted their numbers as to compel them to raise the siege.

The most accurate early description of variola is that of the Bagdad physician, Rhazes, dated about 910 A. D.; but to Avicenna, the Arabian physician (980-1037), belongs the credit of being the first to recognize a difference between small-pox and measles. At about this time also the term *poca,* the Anglo-Saxon equivalent for variola, appears for the first time in a tenth century leech-book attributed to an English physician named Bald. After the introduction of variola into Arabia it became endemic there and appears to have spread to neighboring regions, extending to Asia Minor, North Africa and probably thence to European countries.

According to the writings of one Sigbert von Gemblours, variola appeared in what is now known as France in about the year 541, the epidemic of that year being also described ten years later by Gregory of Tours, who also gave an account of a similar outbreak that occurred in 580 to 582.

From the eleventh century onward an ever-increasing number of records contain descriptions of epidemics of small-pox, the best known of which is that of Constantius Africanus of Carthage, who at Salerno acquainted the physicians of that region with Arabic medicine.

During the twelfth century the crusades with their tremendous outpourings of various peoples were largely instrumental in spreading the disease, the epidemics of these times being of particular virulence.

The Normans are supposed to have introduced variola into England about 1241; at the same time it is also reported from Denmark. On the continent the disorder seems to have become prevalent in Germany in 1493, having probably been imported from the Netherlands; somewhat later it appeared in Russia and Sweden. Epidemics of unusual virulence are reported during 1546-1589 from Italy, France and Holland.

In America, small-pox made its appearance not long after the landing of Columbus. It is reported in Hispaniola (now San Domingo) in 1517; whence it spread to Cuba and the Antilles, and from Cuba to Mexico, through the medium of a Negro slave among troops captured by Navarez and landed in Mexico as prisoners of Fernando Cortez. The ravages of the epidemic that originated in this way in Mexico beggars description. In a short time three and one-half million people are said to have succumbed to the disease.

Once having gained a foothold in Mexico, it was an easy matter for small-pox to spread to other American countries. In 1710, about 60,000 persons are reported to have died of the scourge in Quito, the capital of Ecuador. In North America the African slave trade afforded an additional favorable opportunity for the continued prevalence of variola, a circumstance considered by some to be an important factor in the extermination of the Indians of North America.

Thus no region seems to have been exempt from the ravages of this fearful scourge which respects neither age, nor sex, nor race.

During the seventeenth and eighteenth centuries variola was constantly on the increase, only a favored few being spared an attack of the disease. It occurred mostly among children, adults more rarely contracting the disease because of the immunity acquired from the attack during childhood. Children who had not had small-pox were considered "susceptible," and a case of the disease occurring where a number of such susceptibles were gathered was the starting point of epidemics on many occasions. In the larger European centers the scourge appeared in epidemics of more or less severity in periods ranging from four to six years.

Although writers, as late as the sixteenth century, failed to distinguish variola from measles, they seemed to recognize the contagious nature of the disease. During the following centuries (the 17th and 18th) there gradually arose a better scientific understanding of variola, and to Sydenham belongs the distinction of having made the first differentiation of measles and variola. But at the same time he was not so entirely convinced of the contagious nature of variola, rather leaning to the theory that the disorder was a sort of healing process by which the body in a natural way rids itself of harmful secretions. His therapeutic suggestions were entirely opposed to those in vogue at the time. He recommended a cooling, antiphlogistic treatment which would hasten the outbreak of the eruption, allowing his patients to be out of bed in the fresh air until the eruption appeared; if the patient was unable to be up he insisted upon plenty of fresh air for the sick-room.

Another advocate of fresh air was Boerhave (1668-1738), who also advised the use of cathartics, emetics and cupping for the fever. To this physician belongs the credit for the idea of controlling the spread of variola by isolating the patient. Not only was he convinced of the contagious nature of variola, but he observed that it was carried by the air and entered the body through the respiratory tract. Although isolation in those days was neither largely practiced nor carefully carried out, that it afforded a degree of control for the disease is evidenced from the historic example of Rhode Island, whose laws required that all sufferers from small-pox be isolated on the Island of Coasters Harbor, with the result that from 1740 to 1765 no epidemic of small-pox was known in that State. But, on the whole, quarantining variola victims proved of little avail in the general control of small-pox.

An early German writer jocosely remarks that few escape small-pox and love. This may well be taken to indicate the general resignation with which an attack of small-pox was accepted as one of the inevitable or practically inevitable facts of life. Accordingly, efforts were directed not so much toward controlling the disease as toward devising means of controlling the attack, i.e., making it as mild as possible, and thus gaining immunity for life. The idea of variolation for this purpose is almost as old as the history of variola itself. The method and its evolution into vaccination, as introduced by Jenner, are discussed at pages 191-194. Since Jenner's day small-pox has been decreasing in proportion to the prevalence of the custom of vaccination, thus realizing the vision of Moore, who, in 1815, wrote: "Infectious diseases spring up in obscurity, and extend indefinitely; but if opposed with judgment, they might, like empires, be controlled; and would decline and fall. The small-pox has past through the first stages, and is now sinking into the last."

BIBLIOGRAPHY

CHIARI, H. Ueber osteomyelitis variolosa. Beitr. z. path. Anat. u. z. allg. Path., 1893, xiii, 13.

CHURCHILL, D. The history of small-pox in Rhode Island. Providence Med. Jour., 1902, iii, 131.

COUNCILMAN, W. T., ET AL. Studies on the pathology and on the etiology of variola and vaccinia. Boston, 1904.

——— Small-pox: in Osler's Modern medicine. Philadelphia, 1907, Vol. II.

DREYER, W. Beitrag zur Behandlung der Variola. München. med. Wchnschr., 1910, lii, 1642.

FINSEN, N. Remarks on the red-light treatment of small-pox. Brit. Med. Jour., 1903, i, 1297.

GINS, H. A. Ein Beitrag zur Beurtheilung der Dauer des Pockenimpfschutzes. Deutsch. med. Wchnsch., 1916, xlii, 1155.

HALLENBERGER. Beitrag zur Aetiologie der Variola. Centralbl. f. Bakteriol. u. Parasitenk., 1917, Abt. i, Orig. lxxi, 3; Abstr. Centralbl. f. allg. Path. u. path. Anat., 1918, xxix, 433.

HANNA, W. Studies in small-pox and vaccination. New York, 1913.

JOCHMANN, G. Pocken und Vaccinationslehre. Vienna and Leipzig, 1913.

KER, C. B. Infectious diseases. London, 1909.

KINYOUN, J. J. The serum therapy of variola and vaccinia. Rep. Superv. Surg.-Gen. Mar. Hosp., 1896-7, Washington, 1899, p. 766.

MCCLURE, J. C. Handbook of fevers. London, 1914.

MOORE, J. The history of small-pox. London, 1815.

PFEIFFER, L. Ein neuer Parasit des Pockenprozesses aus der Gattung Sporozoa. Cor.-Bl. d. allg. ärtzl. Ver. f. Thüringen, 1887, xvi, 77; 1888, xvii, 644.

PROWAZEK, S. Untersuchungen über die Vaccine. Arbeit. a. d. k. Gesundheitsamte, 1907, xxvi, 54.

RICKETTS, T. F., AND BYLES, J. B. The diagnosis of small-pox. London and New York, 1908.

RUHRÄH, J. Small-pox: in Forchheimer's Therapeusis of internal diseases. New York, 1913, Vol. II, p. 40.

SCHAMBERG, J. F. Variola: in Musser and Kelly's Practical treatment. Philadelphia, 1911, Vol. II, p. 510.

SCHATZMANN, M. Untersuchungen über die Haematologie der Variola und Vaccine. Cor-Bl. f. schweiz. Aerzte, 1913, xliii, 1515.

SEPTÉT, P., AND MANET, J. Traitement de la variole par l'or colloïdal. Marseille méd., 1917, n. s. No. 20, 608.

THOMSON, R. S., AND BROWNLEE, J. Further observations on the treatment of small-pox by the serum of immunized heifer. Lancet, 1903, i, 947.

UNNA, P. G., JR. Neuere Erfahrungen mit Pockennarbenbehandlung. Berl. klin. Wchnschr., 1914, li, 1685.

VAN DER LOEFF, A. Ueber Proteiden oder Amöben bei Variola vera. Monatschr. f. prakt. Bakteriol., 1887, vi, 447.

WELCH, W. M., AND SCHAMBERG, J. F. Acute contagious diseases. Philadelphia, 1905.

CHAPTER X

VACCINIA

(*Vaccination*)

BY SAMUEL SIDNEY WOODY, M.D.

Definition, p. 215—Relation of vaccinia to variola, p. 215—Symptomatology, p. 215—Mode of onset and normal course, p. 215—Indications for vaccination, p. 217—Technic of vaccination, p. 217—Revaccination, p. 218—Complications and association with other diseases, p. 218—Treatment, p. 219—Historical summary, p. 219.

Definition.—Vaccinia, or vaccination, is a febrile disease acquired only by inoculation with the virus obtained from cow-pox (bovine virus) or from a human subject who has been inoculated against variola (humanized virus), and producing a number of lesions corresponding to the number of insertions.

Relation of Vaccinia to Variola.—The relation of vaccinia to variola has not yet been definitely explained. The accepted theory is that the virus of small-pox is altered during its passage through one of the lower animals, so that it loses its power of inducing small-pox but retains sufficient antibodies to act as a protection against the disease. The identity of the virus of variola and of vaccinia is established by the presence in both, as well as in skin sections of both diseases, of microscopic cell-inclusion bodies, first described by Guarnieri, in 1892, and later confirmed by Pfeiffer, Councilman and others. The studies of these bodies led these investigators to the conclusion that they are protozoa closely related to the etiology of vaccinia and variola. Fornet has described small diplococci which he found in lesions of both diseases and which he believed to be etiologically related to variola. Confirmation of these findings would establish the identity of the two disorders, but that confirmation has not been forthcoming up to the present.

Copeman, of England, and Tyzzer, in this country, have shown by experiments that vaccination protects the monkey against subsequent inoculation with small-pox virus, thus confirming Jenner's early experiments, which demonstrated the efficiency of vaccination by variolation, or the "variolus test."

Symptomatology.—MODE OF ONSET AND NORMAL COURSE.—The incubation period of typical vaccinia, especially after a primary vaccination, is remarkably constant. For the first three days after the operation there is no local reaction except that due to the trauma of the act of vaccination. At the end of the third day, or the beginning of the fourth day, the site or sites of inoculation redden, swell into tiny macules which, within the next twenty-four hours, develop into flattened papules. About the fifth day the pock is surrounded by a small hyperemic areola from which the papule rises like the nipple from the mammary areola. It then changes into a transparent vesicle and reaches complete maturity on the seventh or eighth day, when it presents a full round vesicle with a slight central depression containing a yellowish scab—the tissue from the vaccination scar. On the ninth or tenth day the vesicle becomes pustular and shows definite umbilication. Desiccation then sets in almost at once, the center dries, the crust forms and rapidly grows outward until it covers the entire pustule, falls off (if not disturbed) on the fourteenth to the twenty-fifth day, leaving a reddish scar which in the course of a month or two becomes white and finally leaves a pitted mark.

The reddish areola, widening during the development of the pock and often extending several centimeters beyond it, is one of the most pronounced features of vaccination, and when several such areas develop around three or four sites of inoculation on the same arm, for example, their confluence is apt to be mistaken for erysipelas. But their outlines are much less well defined than those of erysipelatous lesions.

Slight variations from the normal course of vaccinia may sometimes be observed, especially in healthy young children during the hot summer months, or in winter in a heated room, when the pocks develop more rapidly; or in under-nourished children, when apt to develop more slowly. The incubation period may also vary in different pocks on the same individual, some developing more slowly than others. Certain authors have noted a compensatory process in such cases, the slow-growing efflorescences making up by going through the different stages more rapidly, the areola appearing at about the same time in all, and only the papules of the slower ones something lagging. A cachectic reaction is also described as sometimes occurring in anemic children, the areola being indistinct, signs of the same not appearing until the tenth or twelfth day. The papule, however, develops normally. Fever is correspondingly slight or altogether absent.

The *subjective symptoms* comprise intense itching which begins on the third or fourth day after inoculation and is accompanied by more or less severe pain in the arm and perhaps in the axilla, and is again followed by itching during the process of healing. Sometimes on the third or fourth day after the incubation period there is a slight rise in the evening temperature, but as a rule the temperature rises irregularly, reaching its maximum, 101°–104° F. (38.3° to 40° C.), on the eighth day. The pulse, corresponding to the temperature, is more or less rapid, and there may also be general malaise, loss of appetite and of sleep. Adults often complain of headache, languor and sometimes nausea; in children there may be more or less delirium.

Albuminuria during the course of vaccination is very rare, and is then eminently a febrile manifestation. Nephritis is not known.

Among the *anomalies of vaccinia,* due to the inoculation of the vaccine virus elsewhere than at the intended site, are polymorphopostvaccinal exanthem and the eruption—accessory pocks, generalized vaccinia—due to transmission by direct transfer or by way of the blood and the lymphatics (auto-inoculation), and accidental inoculation by transfer of the virus, from the individual vaccinated to a second person.

The postvaccinal exanthem is an urticarial, morbilliform or roseola-like rash, the most pronounced feature of which is violent itching. It appears about the seventh to the fourteenth day after vaccination, beginning on the face, and extending downward to the trunk and the extremities. It can be differentiated from *rubella* by the absence of swelling of the cervical glands, and from *measles* by the absence of Koplik's spots and symptoms of coryza. Jochman attributes this to anaphylactic reaction, since two of the twelve children in whom he observed it were immune, the vaccination failing to take.

Accessory or secondary pocks by *auto-inoculation* may arise around the site of vaccination or in any other part of the body. Some authorities claim that they are due to transmission of the virus through the lymphatics, since they usually develop at a time when the primary vesicles begin to fill with lymph. The pocks usually abort, rarely progressing beyond the papular stage. This is explained by the fact that the patient has already developed a partial immunity which, as it becomes complete, prevents the full development of the pocks. In most instances, however, the *secondary inoculation* is an accidental one *through direct transference* of the virus by means of the fingers or through the careless use of towels which have come in contact with the vaccination pustule. Not only can the vaccinated person inoculate himself in this way, but he may also affect another individual. Conjunctival and also nasal vaccination result from such accidental transference of the virus. Such pustules arising on the eye should be treated with the mildest sort of solutions. They generally heal without leaving any effects, although serious eye trouble may follow.

Indications for Vaccination.—The best time for a primary vaccination is early infancy—between the fourth and the sixth month—when both the local and constitutional reactions are apt to be less severe and there is also less danger of secondary infection. The only contra-indication to early vaccination is, of course, the state of the child's health. If the child is delicate or under-nourished, owing to improper assimilation, or in the presence of an eczema or of syphilis, it is better to postpone the operation until the condition is improved. In case of exposure or during an epidemic it is justifiable to vaccinate a child at any time, taking a chance with the contra-indications as the lesser of two evils.

Technic of Vaccination.—The technic of vaccination is a matter of choice. Some governments require four inoculations; some physicians make three and others only one, selecting either the arm or the leg for the purpose. It is our practice to choose the outer surface of the left arm just below the insertion of the deltoid muscle; sometimes, if desired in females, the leg below the knee may be chosen. After thoroughly cleansing the chosen site with soap and water, followed by alcohol, the site is allowed to dry. The virus is then dropped on the cleansed area, which is then scarified with a blunt lancet, needle or any of the special instruments devised for the purpose. Three or four parallel abrasions 3/16 inch (4.6 mm.) long are made, penetrating the skin just enough to show serum but not to cause bleeding, the virus all the while being rubbed in cautiously so as to prevent the escape of serum or blood. A temporary **shield** is applied only for the purpose of preventing infection or rubbing off the vaccine by the clothing. It should by all means be removed after twenty-four hours, as its further use would be harmful. The shield is easily made of a circular piece of cardboard, somewhat larger than the inoculated area, slit to the center at one point, turned into a cone and fastened with adhesive plaster. The only other local treatment, except in the event of secondary infection, is painting the site twice daily, beginning two days after the operation, with a solution of **iodin,** 1 part; **picric acid,** 4 parts; and **alcohol,** 95 parts. This lessens the chance of outside infection, cuts short the acute stage of the process and in no manner interferes with its efficacy.

At the present time the manufacture of vaccine lymph is carefully carried out and there is no danger of contamination. This does not lessen but rather increases the responsibility of the physician, since with a lymph of known reliability any accident is directly due to faulty technic; that is to say, lack of proper cleanliness of his hands, sterilization of instruments and dressings. Nor does his duty end with the operation. The patient should be **kept under observation** for indications of possible secondary infection.

Vaccination is without doubt one of the greatest blessings that medical science has given mankind; but there is still considerable opposition to the method, and it is the duty of the medical profession to do nothing that will discredit it in the eyes of the public.

Revaccination.—The protection afforded by a primary vaccination, although it is never entirely nullified, gradually diminishes, so that it is desirable to revaccinate children at the age of seven to ten years and at adolescence, and during adult life as occasion arises through exposure to the risk of contagion, or as a preventive measure during an epidemic. There are no contra-indications to vaccination during an epidemic or after a known exposure to small-pox. In the interest of public health vaccination, if it is not already compulsory, should be insisted upon at every such occasion. If this were practiced everywhere variola would soon disappear from the face of the earth.

The course of revaccination often deviates from that of a primary inoculation. On about the second day there is local reddening and irritability; the papules appear on the third or fourth day and may or may not develop into vesicles and pustules. Very often revaccination fails altogether; in such instances it is advisable to repeat the inoculation with a different virus, if possible, before definitely concluding that the subject is insusceptible.

Complications and Association with Other Diseases.—Vaccination, though it generally runs a perfectly normal and benign course, may be associated with complications, the most important of which are *tetanus* and *erysipelas.* Neither of these, however, is peculiar to vaccination, since either may result from infection from any skin lesion. And in so far as carelessness in the operation and possible abrasions of the skin lesions of vaccinia—especially in a weakened individual—offer convenient portals of entry for all kinds of bacteria, it might be said that vaccinia may be associated with any of the various types of infection. Some antivaccinationists claim that *syphilis, tuberculosis* and *leprosy* may be acquired through inoculation with the vaccine virus. The use of glycerinated calf lymph should in all instances absolutely prevent any such occurrence, since experiments show that neither the tubercle bacillus nor the streptococcus of erysipelas are able to survive prolonged exposure to the action of 50 per cent. solution of glycerin in water; and, furthermore, the calf does not acquire either syphilis or leprosy.

The normal course of vaccination may also be complicated by an intercurrent acute infection, such as *measles, scarlet fever, whooping-cough, varicella, influenza,* without, however, affecting either the vaccinia or the superadded infection. The one exception to this ruling may possibly be *diphtheria,* where prognosis is sometimes unfavorably affected when it accompanies vaccinia.

As to the question of vaccinating a patient already suffering from one of the acute infections, it is our feeling that these patients have all they can do to throw off the illness from which they are suffering and that if at all possible vaccination should be postponed until recovery has taken place. This is particularly true of *scarlatina,* where the skin is already devitalized and the air of a scarlet fever ward is charged with organisms—especially streptococci. Under these conditions secondary infection is liable to occur. We believe that nothing should be done that may prejudice the public against so eminently a beneficent procedure as vaccination and, we repeat, unless absolutely imperative it should not be done under adverse conditions.

Treatment.—Little is required in the way of general treatment of vaccination, except during the *febrile stage,* especially in young children, when **rest in bed, light diet** and **attention to the bowels** are indicated. A **fever mixture** may be given, if necessary, but ordinarily little more will be needed. Any marked constitutional symptoms should suggest secondary infection, the treatment of which is the same as for any wound infection after abrasions or other injuries to the skin.

Historical Summary.—The precursors of Jenner's protective prophylaxis against variola date back to ancient and medieval times. The observation, that individuals who had recovered from small-pox never suffered a second attack, led to the supposition that the artificial production of a mild form of the disease (variolation) might have the same result. The most primitive type of such variolation is that practiced by the Chinese, who mixed the crusts of variola pustules with musk, wrapped them in cotton, and after they had been kept for years and treated with vapors of all kinds and with medicinal herbs in order to attenuate their virulence, were inserted into the nostril of the person to be protected. It was also customary for the individual to don a shirt which had been smeared on its inner surface with the pus of the variola pustules.

Somewhat more logical was the Brahmin manner of variolation practiced in India. This consisted in introducing the material from a variola sore into the skin on the upper arm by means of a needle, making fifteen or sixteen scarifications and covering the scarified area with a tuft of cotton which had been dipped in variola material, and sprinkling it with holy water from the Ganges River. The pock material used was always at least one year old and was taken from an inoculated individual, not from a case of spontaneous small-pox. The patient was obliged to remain in the open air and to avoid intercourse with his fellowmen, and to restrict his diet to fruits, rice and light food.

Needle puncture was also the method used in other oriental countries—Persia, Armenia, Circassia, Georgia, etc. The Circassians and Georgians, in order to make sure of results, used three needles tied together and pricked the body in several different places when introducing the variolous material. In all these countries the practice was called "buying the small-pox," the origin of which is supposed to be the custom of giving the child to be inoculated a few raisins, dates or sweets to carry in his hand and, showing them to the child from whom the material is to be taken, asking how many pocks he will give in exchange for the sweetmeats. This practice spread among the common people along the coast of Africa and even passed over into European countries, Italy, France, Germany, Sweden, Denmark and South Wales.

The first accounts of the oriental mode of variolation came to Europe through the writings of a Greek physician, Timoni. This consisted in inoculating the fluid contents of variola vesicles into the arm of the recipient through a needle puncture which produced a mild form of the disease with pustules scattered over the body. The impulse to the use of the method was given by Lady Wortley Montagu, the wife of the English Ambassador to Constantinople, who, in letters to friends, enthusiastically described the procedure and advocated its use after her two children had been successfully treated. This mode of variolation, however, fell far short of the ideal one, for it not only produced the disease with most of its serious features, but also provided a means of spreading contagion which not infrequently proved to be the starting point of an epidemic.

It was reserved for Edward Jenner, a simple country doctor, to present to a waiting world the ideal prophylaxis against small-pox, which represents one of the signal triumphs of preventive medicine, the benefits of which it is impossible to over-estimate.

For a long time it was a well-known fact that cow-pox, formerly much more common during pandemics of variola than at present, was transferable not only from one animal to another but also to man. Dairy hands became infected from the udders of cows through slight abrasions or excoriations on the skin of the hands, where they developed small vesicles which, after progressing into pustules, dried up. Similar lesions arose at other sites on the body, but only if transferred from the original one by means of the fingers. The disease, however, was purely a local one unaccompanied by any general exanthem.

Long before Jenner's time it had been generally observed that persons recovered from cow-pox were subsequently immune to true variola. Jenner, the son of an English clergyman in Berkeley, England, while a student of medicine in 1768, overheard a milkmaid say that she could not get small-pox because she had had cow-pox. The remark made a deep impression on the young student, who from that time continually occupied himself with the relationship of cow-pox and variola. During a period of over twenty years Jenner collected and correlated all existing observations and experiments on prophylaxis of small-pox and, by means of personal experiments, endeavored to solve the question. He began by inoculating sixteen individuals, who at a more or less remote period had had cow-pox, with the lymph from genuine variola, and in all cases he failed to obtain variolation—the inoculated individuals all being immune. His next step was a decisive one and entirely original in the annals of medicine. On May 14, 1796, Jenner inoculated an eight-year-old boy, named James Phipps, with the lymph of cow-pox taken from the hand of a milk-maid, Sarah Nelmes, thus establishing the first instance of inoculation with human lymph. The result was typical cow-pox in the boy. Jenner then resorted to the crucial test of inoculating the same boy with the lymph of genuine variola, which, according to his expectations, proved negative, i.e., variola did not develop. The first test, made on July 1, 1796, was followed a few months later by a second one, with a similar negative result. He was thus enabled to demonstrate for the first time that the lymph of cow-pox is transferable not only from the cow to man, but also from man to man, and that the transference of humanized vaccine confers the same protection against variola as the natural lymph of cow-pox. It was not, however, until after repeated successful experiments that Jenner finally, in 1798, published the results of his epoch-making discovery. The benefits of vaccination have since accrued to mankind everywhere, for vaccination is practiced to-day in virtually all civilized communities, and, in most localities where it is not compulsory, it is at least a prerequisite for admission to schools, institutions and to some business houses.

Vaccination was introduced into the United States during the year 1800. In July of that year Dr. Benjamin Waterhouse, Professor of Physics at Harvard University, vaccinated his own children, and at about the same time Dr. John Redman Coxe, of Philadelphia, vaccinated his oldest son, and in order to test the experiment boldly exposed him to small-pox contagion. The exhibition of the child's total immunity did much to establish confidence in Jenner's method and to introduce it throughout the country.

That Jenner and his supporters should have been subjected to much unpleasant criticism and opposition is not surprising, but that there should still be those who systematically oppose the practice seems incredible in this twentieth century, when the boon of this discovery has become apparent in the waning and in the possibility of the ultimate eradication of variola from the arena of medicine, though unfortunately it is too true. Councilman has well described this peculiar type of individual who makes up the antivaccinist: "Small-pox can, but probably never will be wholly eradicated. The chief obstacle which stands in the way of its eradication is an inability to recognize facts, and to make the proper deductions from them, which seems to be associated with certain orders of mind. The facts with regard to the production of small-pox immunity by vaccinia are perfectly established. The order of mind which leads to their denial will probably never disappear from the human race."

BIBLIOGRAPHY

COPEMAN, S. M. The Milroy lectures on the natural history of vaccinia. Brit. Med. Jour., 1898, i, 1185.

——— The pathology of vaccinia. Pub. Health, 1894-5, vi, 108.

COUNCILMAN, W. T., McGRATH, G. B., BRINCKERHOFF, W. R., TYZZER, E. E., ET AL. Studies on variola and vaccinia. Boston, 1904.

CROOKSHANK, E. M. Vaccination, its history and pathology. London, 1889.

FITZGERALD, J. C. A case of generalized vaccine. Pub. Health, 1918, ix, 278.

FORNET, W. Die Reinkultur des Variola-Erregers. Tr. Internat. Cong. Med., 1913, London, 1914, Sect. iv, Bacteriol. and Immunol., pt. 2, 119.

GUARNIERI, G. Ulterioro recherche sulla etiolgia, sulla patogensi della infezione vaccinia. Clin. mod., 1897, iii, 57.

JOCHMANN, G. Pocken und Vaccinationslehre. Leipzig, 1913.

KOLMER, J. A. Infection, immunity and specific therapy. Philadelphia, 1917.

MOORE, J. The History of small-pox. London, 1815.

PFEIFFER, E. Ueber die Züchtung des Vaccinerregers in dem Cornea-epithel des Kaninchens, Meerschweinchens und Kalbes. Centralbl. f. Bakteriol. u. Parasitenk., 1895, xviii, 769.

TYZZER, E. E. The etiology and pathology of vaccinia. Jour. Med. Res., 1904, xi, 180.

CHAPTER XI

VARICELLA

(*Chicken-pox*)

By Samuel Sidney Woody, M.D.

Definition, p. 223—Etiology, p. 223—Symptomatology, p. 224—Diagnosis, p. 225—Differential diagnosis, p. 225—Complications, p. 226—Sequelæ, p. 227—Association with other diseases, p. 227—Clinical varieties, p. 228—Treatment, p. 228—Prophylaxis, p. 228—General management, p. 229—Management of convalescence, p. 230—Prognosis, p. 230—Pathology, p. 230—Historical summary, p. 231.

Definition.—Varicella or chicken-pox is a highly communicable, mildly acute, exanthematous disease, characterized by a long incubation period, feverishness and a vesicular eruption appearing in crops and drying up in a few days with or without leaving pitted marks.

Etiology.—The disease is disseminated over the entire world, is endemic in large cities, epidemic at times, but generally considered to be more prevalent in the autumn months. It is eminently a disorder of childhood with no discrimination with regard to race, and little, if any, as to sex. Adults, however, are not entirely immune, as many as six per cent. in a series are reported to occur after puberty. We have observed it in a man 64 years of age; others report their oldest case at the fiftieth year. It is rarely seen before the sixth month after birth, although instances are recorded of new-born infants developing varicella as early as the eleventh to the fourteenth day, having been infected from the mother. The period of greatest susceptibility occurs between the fourth and the tenth year of life.

The virus of varicella is not known, nor is the mode of communication definitely established. Experience indicates that it can be transmitted by a third party and also by aërial convection. Indeed, we find that it is the one disease that can be communicated from ward to ward in a hospital and even from building to building, in spite of the most painstaking efforts to prevent its spread. It is transferable from the moment of onset of an attack, but unlike the virus of variola, the varicella virus is short-lived, so that infection by fomites is more or less doubtful.

Tyzzer, in a study of the histology of the skin lesions of varicella, observed certain inclusion bodies in the cell-nuclei and the cytoplasm, which he was inclined to think specific, but failure to produce new lesions by inoculation with the bodies forced him to conclude that they were not parasitic. Keyssellitz and Mayer also observed similar bodies which they believed analogous to cytoryctes, and, although non-parasitic, contained the infective virus.

Symptomatology.—The varicella eruption usually appears on the fourteenth day after exposure to the disease, but it has been known to develop as early as the eleventh day. In our experience the *incubation period* has been prolonged to the twenty-second day, while some authorities report an incubation period of thirty days after a known contact.

Prodromal symptoms are often entirely wanting and when present are slight, the eruption (especially among private patients) being generally the first sign of the disease. Observations in the scarlet fever and diphtheria wards of a fever hospital usually show that more or less fever precedes the eruption by several hours or even a day or two. The temperature may go as high as 104°–105° F. (40°–40.6° C.) and may be accompanied by depression, languor, loss of appetite and nocturnal restlessness. Exceptionally the early symptoms are more aggressive, extending over a period of four or five days, accompanied by malaise, backache, abdominal pain, vomiting, epistaxis. But marked symptoms do not presage a severe attack and vice versa. In the adult the prodromal symptoms are apt to be severe and prolonged, quite often simulating those of variola and confusing the diagnosis.

Some authors describe an urticarial, a morbilliform or a scarlatiniform rash. Our experience is confined entirely to the scarlatinal prodromal rash. The eruption is apt to be punctate, often so closely resembling that of true scarlet fever as to send the patient to the scarlet fever ward, only to have the varicella eruption develop a few hours later. Other cases suggest a scarlatino-varicella infection and prove to be varicella. The rash produces no general symptoms although, according to some writers, it is accompanied by burning sensations, headache, dizziness, joint pains and slight difficulty in swallowing. It generally disappears in about twenty-four hours.

The eruption usually begins on the covered parts of the body, the back, sometimes the scalp, and spreads to the face, the rest of the trunk, and the extremities, preferably their proximal portions; not infrequently it also attacks the mucous membrane of the mouth, the pharynx, the larynx and that of the genitalia.

At first the efflorescences appear as small pink spots which soon become papular and vesicular; but often they abort and never develop beyond the first or second stage. The eruption appears in successive crops, so that efflorescences can be observed at the same time in all stages of development from the macular to the desiccating scab stage. The vesicles are thin-roofed and rupture easily on pressure. They may vary in number from ten to several hundred or thousand; in size they may range from that of a pin-head to a diameter of 10 mm., the average being that of a pea; pemphigus-like sores as large as a silver dollar have also been observed. The vesicles at first contain a clear fluid which becomes pearly and turbid just before they begin to dry up. Sometimes an *irregular reddish areola develops around the base of the vesicles, giving them* the appearance of variola lesions. Very often, especially in undernourished children, the vesicular contents becomes purulent, secondary infection of which may lead to ulceration persisting for several weeks.

The eruption runs a mild course, the vesicles beginning to dry up in a day or two. But owing to the fact that they develop in crops, the desiccation process is generally prolonged over five or six days; in fact, two to three weeks is often required for the completion of the entire process. The crusts that form are shed and leave a reddish-brown stain, or in some instances a tiny umbilication from destruction of the true skin.

Even in the mildest sort of case the varicella eruption may attack the mucous membrane of the mouth, the hard palate, the tongue, the gums, as well as the tonsils and the pharynx, and also the external genitalia. As a rule, the only discomfort caused by the spots in the mouth and throat is a little difficulty in swallowing or in masticating. Inflammatory infiltration, however, may lead to secondary stomatitis, burning sensation in the throat, tonsillitis with general symptoms including orchitis (in the male). Perforation of the soft palate from an ulcerating varicella lesion has been reported. Occasionally the eruption involves the larynx and gives rise to croup-like symptoms (croupous varicella) which may require intubation or tracheotomy. When inspection of the larynx is not possible in such cases and diphtheria cannot be definitely excluded, it is well to be on the safe side and administer diphtheria antitoxin.

The *temperature* even when it has been high during the period of invasion generally falls to the normal in the course of one to three days. In rare instances fever may persist five or six days, and in small children may be marked and accompanied by a very profuse eruption. Secondary infection of varicella lesions may prolong the febrile period for two or three weeks.

After the eruption is well established there are practically no constitutional symptoms except perhaps itching, caused by contact of the skin with the clothing.

Diagnosis.—The diagnosis of the typical case of varicella presents little difficulty. The long incubation period, the absence or mildness of the prodromal symptoms, the appearance of the eruption in crops and the moderate fever are the common features of the disorder. In certain instances, however, it is difficult, if not impossible, to differentiate.

DIFFERENTIAL DIAGNOSIS.—*Variola.*—The one condition of importance with which border-line cases may be confused is variola, especially in its milder form or when modified by more or less remote vaccination and when occurring in the adult. The importance of arriving at a positive diagnosis is readily apparent. Failure to do so may result disastrously to the community in general and to the attending physician in particular. A history and evidence of successful vaccination in a child, and vaccination within a period of six or seven years in the adult would ordinarily speak in favor of varicella. In the absence of such a history it should be remembered that variola is generally preceded by a three days' prodromal stage accompanied by high fever and severe backache, and that the eruption begins, preferably, on the exposed surfaces, the face, the arms, the back, the lower extremities, especially the distal portions. It is also generally more abundant on the shoulders than over the loins and more profuse on the chest than on the abdomen, while the varicella eruption shows no such constant differences. In variola the density of the eruption increases from above downward (centrifugal distribution), while the density of the varicella rash increases from below upward (centripetal distribution). The lesions of variola lie deep among the epidermal cells, while the lesions of varicella are superficial. The variola lesions at first present firm papules which increase slowly in size and develop into vesicles and pustules. They are circular in outline, while the varicella lesions are oval, jagged and irregular, are never actually indented and are soft and velvety to the touch. The variola lesions, on the other hand, are frequently indented and are tense and firm.

Impetigo.—In the desiccating stage the differentiation between *impetigo* and varicella may have to be made. Usually the presence of varicella lesions in the vesicular stage settles the doubt. The pustules and crusts of impetigo are usually more profuse on the face than elsewhere, while the lesions of varicella, even if profuse on the face, are oval in outline. However, it may happen that all the lesions have developed beyond the vesicular stage and owing to the crusts having formed and reformed several times they will have lost their oval shape. In such instances differentiation would be almost impossible and it is well to entertain the suspicion of impetigo and isolate the patient.

Pemphigus.—Early pemphigus where the bullæ are small may possibly be mistaken for varicella, but, as a rule, the large sores appear promptly and clinch the diagnosis.

Complications.—In so benign a disorder as varicella, complications are not likely to occur, although they are not excluded. When they do take place they are generally associated with the skin lesions, any abrasions of which present favorable avenues for the entrance of all kinds of bacteria—pyogenic and others. The most important of such complications is erysipelas, which may develop about the efflorescences—especially the deep-seated ones—and may be so severe as to cause death. In neglected cases especially, an impetigous inflammation on the scalp may result from scratching a vesicle and, owing to the want of cleanliness, lead to local eczema. In rare cases a gangrenous dermatitis—often considered a variety of the disease but in reality a complication—may result from ulceration of infected vesicles, especially those at or near the external genitalia.

A varicella vesicle on the eyelid may lead to severe conjunctivitis, but usually it provokes only a marked edema. Very occasionally the eruption involves the cornea, producing ulceration and opacity, or more deep-seated lesions, may result in panophthalmia and destruction of the eye.

Simple and suppurative adenitis have been reported while nephritis, though not common, is a sufficiently frequent complication of varicella to warrant careful management to prevent its occurrence. It may complicate the mild as well as the more serious cases, and usually appears on the eighth to the fourteenth day of the disease. In pronounced cases the nephritis may be associated with fever, albuminuria and all the severe manifestations of true scarlatinal nephritis. The prognosis, however, is favorable, as it usually subsides in about two weeks' time and leaves no permanent effects. Arthritis, synovitis, disturbances of the central nervous system—myelitis, encephalitis, otitis media—are sometimes mentioned as complicating varicella, but they are exceptional. Gastro-intestinal disorders—particularly appendicitis—are also reported as complicating the disease, but by the majority of the profession they are regarded as incidental phenomena.

Pulmonary complications—bronchitis, bronchopneumonia—occasionally develop during an attack of varicella, especially when it enters as a cross-infection in whooping-cough or measles.

Sequelæ.—It is only natural that a benign disease that presents few complications should be equally devoid of sequelæ. Jochmann mentions the influence of varicella in arousing latent tubercular conditions, especially of the glands or the lungs, and the possibility of the development of miliary tuberculosis. But such instances are as rare as any other sequelæ of varicella.

There is an impression that the varicella patient shows a particular susceptibility to scarlet fever, due, no doubt, to the possibility of an abraded varicella vesicle as the avenue for the scarlatinal infection. On the other hand, the presence of any of the infectious diseases, such as scarlatina, measles, whooping-cough and others, does not affect the susceptibility to varicella, but the weakened condition of the patient may influence the course of the superadded disease and lead to suppuration and ulcerative degeneration of the varicella efflorescences.

Association with Other Diseases.—A question that has of late been receiving considerable attention is the relationship between varicella and herpes zoster. The association of the two diseases was first pointed out by Bokáy in 1892, who, several years later, reported nine observations. Le Feuvre, in 1914, had collected thirty-eight reports, including several personal observations, many concerning several instances seen by one and the same author. Other observations have been recorded from time to time, among them the 3 cases recently reported by Goldberg and Francis, and 3 by Low, the total number being now well over 50 (Low). In the majority the varicella eruption develops without any other demonstrable source of contagion than an existing case of herpes zoster; in others the herpes follows after the varicella, the latter infecting contacts after the usual incubation period; and in some few the herpes is followed in the same individual by a varicella eruption. For this aberrant eruption (of herpes) Le Feuvre suggests the name varicella herpetica. Low is strongly inclined to the conclusion that the two diseases are due to the same virus, which may belong to the ultramicroscopic filterable group of organisms. He suggests that in herpes, infection is probably local through the nose, that is, the lymphatics around the olfactory nerves, similar to that of epidemic poliomyelitis, with which it has many points of analogy. The virus after reaching the meninges and the cerebrospinal fluid easily gets to the ganglia of the sensory nerve trunks. In varicella there is a blood infection with the virus, and in those cases which simultaneously present the two eruptions, the virus probably first attacks the ganglia and then, three or four days later, gets into the blood and produces a general eruption.

The question of *immunity* is interesting in this connection. One attack of varicella conveys immunity for life, second-attacks being most unusual, if at all possible. If herpes zoster and varicella are due to the same infectious agent it would be reasonable to suppose that an attack of one disease would provide immunity against the other. According to Low, however, it appears that herpes zoster protects against varicella, but varicella does not protect against herpes. Adults that have had varicella in childhood develop herpes, but he finds no instance of a case of herpes which developed varicella later on, and in no case of herpes associated with a generalized varicella eruption was there a history of a previous attack of varicella.

Clinical Varieties.—The clinical varieties of varicella, like the complications, also concern variations in the skin lesions. In addition to *gangrenous* dermatitis (already mentioned) the eruption may be *confluent,* and *hemorrhagic.* Confluent varicella is rare. The lesions may be multilocular, and the skin edematous, and fever may supervene if pustulation takes place. The hemorrhagic type is also not common. Hemorrhage, either purpuric or petechial, may take place into the skin and subcutaneous tissues, or the efflorescences may become hemorrhagic, with discoloration of the skin due to extravasated blood; hemorrhage may also take place from the affected membranes. Hematuria has also been noted.

Treatment.—PROPHYLAXIS.—**Isolation** of the patient *is neither imperative nor really practical.* The disease is a benign one and is not worth the inconvenience which, owing to its highly communicable character even in its earliest stage, would be required to make quarantine effective. Contacts need not be detained for more than three weeks; infection so rarely occurs later, that longer detention is unjustifiable. To prevent unnecessary loss of time at school contacts may be permitted to attend school for ten days following the first exposure. They should then be kept at home until there seems no danger of developing the disease. Prophylactic **vaccination** has been attempted with varying degrees of success by Kling, Handrick, Rabinoff, Rutelli, Hess and others. Kling (in the service of Medin of Stockholm), although not the first to make the attempt, was the first to report results in a considerable number of cases. During an epidemic (1913) in an orphan asylum he inoculated 58 children with lymph from a clear varicella vesicle collected on a lancet and rubbed into a scarified area on the arm; only 1 of the children developed chicken-pox; 31 showed lesions at the site of inoculation, consisting of red papules which rapidly developed into typical vesicles and dried up in two or three days; 6 children developed papules with occasional vesicles. Of 64 children that were not vaccinated 44 developed varicella.

Rutelli as well as Rabinoff report similar success. The latter observed an incidence of 6 to 8 per cent. among vaccinated, against 75 per cent. among unvaccinated children, inmates of an orphan asylum and all subject to the same conditions of exposure. She furthermore noted that in those that developed the disease although its course was not affected by the inoculation, the incubation period was shorter than usual and that, contrary to previous experiences in eight other epidemics, no second outbreak of the disease took place. Handrick, on the other hand, observed the disease develop in 35 per cent. of 127 children inoculated, so that he is inclined to doubt the value of the method. In only 3 instances did he obtain a local reaction at the site of inoculation which, however, did not prevent the development of a generalized eruption.

Kling makes his inoculation through a small puncture, Rabinoff makes several small scarifications. Handrick used both Kling's method as well as the method of von Pirquet in giving the tuberculin test. Rutelli made the inoculation on a scarified area on the abdomen and obtained marked local reaction in all the 15 cases, one infant developing a small abscess on the twentieth day. Hess, on the other hand, finds these simpler methods less satisfactory than the intravenous injection of a solution of the fluid from a varicella vesicle in normal saline. Of 38 children thus immunized only one developed the disease and that 36 days after the injection. No general reaction is reported by any of the authors.

GENERAL MANAGEMENT.—Very little is required in the treatment of varicella except **rest in bed** until the lesions are well past the acute stage. In the presence of fever the **diet** should be light and, if necessary, a **fever mixture** may be prescribed.

The general treatment of varicella is purely **symptomatic.** The patient should be **kept in bed** until the crusts have fully formed and until the temperature has been normal for several days and examination of the urine proves it to be negative. The only real danger of varicella is secondary infection through the lesions. To avoid this, **cleanliness** is important. The patient's hands, especially the finger-nails, must be kept clean and the latter closely trimmed, and should be tied in padded mittens or stockings. It may at times be necessary to prevent scratching by restraining the arms and legs. *Itching* can be controlled by means of **tepid baths** or by **sponging** with alcohol well diluted with water or vinegar water, three parts to one, followed by a **dusting powder** consisting of the following:

℞

Mentholis	ʒ ss	(2 grams)
Zinci oxidi	ʒ i	(4 grams)
Pulv. amyli	℥ i	(32 grams)
Talci	℥ i	(32 grams)

Should *secondary infection* occur the usual local and constitutional treatment must be instituted. Thick infected scabs or crusts should be softened and removed by **applications of olive oil or poultices.**

For the resulting ulcer **an ointment of ammoniated mercury** may be employed, or better still, an **evaporating lotion** as follows:

℞

Pulv. calaminæ	ʒ ii	(8 grams)
Zinci oxidi	℥ ss	(16 grams)
Glycerini	℥ i	(32 grams)
Liquor calcis	f ℥ ii	(60 c.c.)
Aquæ rosæ	f ℥ viii	(240 c.c.)

Gangrenous dermatitis should be treated by supportive measures, such as **fresh air** and **liberal feeding**; **tonics, cod-liver oil and malt,** and **stimulants** may also be required. For the local treatment of the gangrenous skin lesions we advise that only the **blandest kind of solution** be used; strong solutions we believe are contra-indicated.

The mouth lesions are treated by any of the **bland mouth washes.** Ulcerations will require suitable treatment, such as recommended for ulcerative mouth conditions of scarlet fever.

Special attention should be paid to **general cleanliness.** The **bed-clothing and underwear** should be changed frequently. The patient should be given a **daily sponge bath,** and particular care taken to keeping all lesions, especially those on the external genitalia, clean.

MANAGEMENT OF CONVALESCENCE.—The patient may be considered cured when the separation of the scabs is complete. In the average case, where there is no secondary infection, about three weeks' time will be required for the process. Any crusts that have reformed need not be considered infectious. In such instances it is necessary only to **remove the crusts and carefully cleanse the resulting ulcer,** by touching it up with a **reliable antiseptic solution.**

Prognosis.—The prognosis of varicella is altogether favorable and is not affected by complications such as nephritis, laryngitis or secondary pyogenic infection, should they occur. The bright outlook is marred only when the varicella appears as a superadded infection in a patient already weakened by previous disease—whooping-cough, measles, scarlatina, diphtheria. In such circumstances the varicella is apt to develop seriously and the resulting sepsis may lead to gangrenous dermatitis, pulmonary disease, etc., which often threaten life, and in about five per cent. of cases of such cross-infections are the actual cause of death.

Pathology.—The pathology of varicella is practically limited to the skin lesions. Unna has described the conical lesions as having a tent-like form with lateral walls rising obliquely from a broad base towards the center of the covering composed of a few horny stretched scales. From this covering cellular septa radiate downwards, in contrast to the lesions of variola where the cellular partitions radiate from a central point on the floor of the lesion. In varicella the cavity proper is limited below by the deeper strata of the prickle layer which shows pathological changes. In the center the cavity extends deeper to the level of the swollen and enlarged papillæ which are covered with one or two layers of modified epithelium and project into the cavity. The acute character

of the eruption in varicella is evidenced by the comparatively slight septate cavities due to the rapid distention of a few liquefied cells. The rapid formation of the vesicles which are unilocular, accounts for their thin roof and superficial position.

The latter together with the absence of suppuration and the early repair of young epithelial cells explains the absence of general scarring after a varicella eruption.

Historical Summary.—The first definite description of varicella is that given by Vidus Vidius (about 1626), who also gave it the designation crystalli, or variolæ crystallinæ, or ravaglione, the term still retained by the Italians. It is supposed at that time to have been differentiated from variola, but the evidence is doubtful. Morton (1694), who refers to it as *variolæ admodum benignæ,* and his contemporaries regarded it as a mild type of variola, a theory which prevailed until Fuller (1730) demonstrated the distinct character of the disease. This duality of the two diseases was generally accepted until toward the middle of the nineteenth century Hebra, one of the foremost dermatologists of his time, revived the 'unity' theory of varicella and variola. On account of his eminent position he found many adherents, and it was not until the virulent and widespread epidemic of variola during the years 1871 to 1874 that the question of the dual character of the two disorders was definitely settled and universally accepted.

BIBLIOGRAPHY

von Bokáy, J. Ueber den ätiologischen Zusammenhang der Varizellen mit gewissen Fällen von Herpes zoster. Wien. klin. Wchnschr., 1909, xxii, 1323.

Campbell, D. C. A case of hemorrhagic varicella. Canad. Med. Assn. Jour., 1915, v, 610.

Goldberg, B., and Francis, F. D. Herpes zoster and chicken-pox. Jour. Amer. Med. Assn., 1918, lxx, 1061.

Handrick, E. Schutzimpfung bei Varicellen. Monatschr. f. Kinderh., 1914, xiii, 242.

Hepworth, J. Herpes zoster and varicella. Brit. Med. Jour., 1914, ii, 629.

Hess, A. F. A protective therapy for varicella and a consideration of its pathogenesis. Arch. Pediat., 1918, xxv, 378.

Jochmann, G. Lehrbuch d. Infektionskrankheiten. Berlin, 1914.

Ker, C. B. Infectious diseases. London, 1909.

Keysselitz, G., and Mayer, M. Zur Aetiologie der Varicellen. Arch. f. Protistenk., 1909, xiv, 113.

Kling, C. A. Ueber Schutzimpfung gegen Varicellen. Berl. klin. Wchnschr., 1913, l, 2083.

——— Technic der Schutzimpfung gegen Varicellen. *Ibid.*, 1915, lii, 13.

Le Feuvre, W. P. Varicella herpetica. Guy's Hosp. Gaz., 1918, xxxii, 101.
Herpes zoster and varicella. Brit. Med. Jour., 1915, i, 15.

Lereboullet, P., and Moricaud, I. Varicelle du nouveau-né par contagion maternelle. Arch. de méd. des enfants, 1914, xvii, 288.

Lesné, E. Appendicite aiguë au cours de la varicelle. Bull. Soc. d. pediat., 1913, xv, 491.

Low, R. Cranston. Herpes zoster, its causes, and association with varicella. Brit. Med. Jour., 1919, i, 91. (Gives complete bibliography.)

MILLER R., AND DAVIDSON, J. A. The nervous complications of varicella. Brit. Jour. Child. Dis., 1914, ci, 15.

PÉRIER, E. Appendicite aiguë au cours de la varicelle. Ann. de méd. et chir. inf., 1914, xviii, 213.

RABINOFF, S. R. Prophylactic vaccination for varicella. Arch. Pediat., 1915, xxxii, 651.

RICHARDSON, G. The relationship between herpes zoster and varicella. Lancet, 1913, ii, 1732.

RICKETTS, T. F., AND BYLES, J. B. The diagnosis of small-pox. London, New York, etc., 1908.

RUHRÄH, J. Varicella: in Forchheimer's Therapeusis of internal diseases, Vol. ii, p. 109, New York, 1913.

RUTELLI, G. Vaccinazione profilattica contro la varicella. Pediatria, 1916, xxiv, 328.

SMITH, D. C. W. Acute myelitis following varicella. Amer. Jour. Dis. Child., 1915, l, 445.

SWOBODA, N. Varizellen: in Pfandler and Schlossmann's Handb. d. Kinderh., ii, 121, Leipzig, 1910.

TYZZER, E. E. Histology of skin lesions in varicella. Jour. Med. Res., 1906, xiv, 361.

WHITAKER, A. J. Hemorrhagic chicken-pox. Brit. Med. Jour., 1915, i, 15.

CHAPTER XII

SCARLET FEVER

By Samuel Sidney Woody, M.D.

Definition, p. 233—Etiology, p. 233—Predisposing causes, p. 233—Exciting cause: The organism, p. 235—Symptomatology, p. 239—Clinical history, p. 239—Laboratory findings, p. 243—Diagnosis, p. 243—Complications and sequelæ, p. 246—Relapses, recurrences and second attacks, p. 250—Association with other diseases, p. 251—Clinical varieties, p. 252—Treatment, p. 255—Prophylaxis, p. 255—General management, p. 260—Serum therapy, p. 270—Prognosis, p. 271—Pathology, p. 272—Historical summary, p. 277.

Definition.—Scarlet fever is an acute, contagious, self-limited disease characterized by sudden onset, a pharyngeal inflammation of varying degrees of intensity, a diffuse scarlet eruption, and desquamation in scales, shreds or casts.

Etiology.—The specific cause of scarlet fever is still a matter of conjecture. But in every instance it is dependent upon infection, by contact or otherwise, from a preëxisting case of the disease.

Predisposing Causes.—*Climate.*—Scarlet fever occurs in all parts of the world, although zones of immunity are known to exist. According to Minor, to whom we are indebted for much of our information with regard to the distribution of scarlet fever, such zones are found for the most part near the tropics, where the high temperature combined with periods of great humidity are unfavorable to the development of a tendency to scarlet fever. In this country such a zone of comparative immunity is located between the 30° and 35° latitude North, comprising the states of South Carolina, Georgia, Alabama, Mississippi, Louisiana, Texas. In general epidemics, however, the disease occurs at all points within these zones.

Season—Altitude.—The effects of seasonal influences vary in different regions. In the countries of Western Europe most epidemics occur during the autumn months, while in the United States the late winter and early spring months seem to be the favored ones. The same holds true with regard to the seasonal mortality statistics. Minor also points out that high altitudes are more favorable to the development of a scarlatinal tendency than low ones.

Sex.—Sex does not play a great part in the etiology of scarlet fever, although the male, especially after the tenth year of life, seems to be slightly more susceptible than the female sex.

Age.—As to age, the tendency to scarlet fever is small at the extremes of life. Infants are rarely affected and individuals after the sixth decade are also generally immune, although scarlet fever among the aged is not unknown. The disease occurs preferably between the third and the tenth years, the curve reaching its apex at about the fifth yeaı of life, with a gradual descent until the fifteenth year is reached and a decided decline after that.

Race.—There seems to be a certain correspondence between the zones of comparative immunity to scarlet fever and the racial immunity to the disease. Negroes and dark-skinned races are decidedly less liable to it than the white race. In the United States this immunity is six times greater among the negro than among the white population, i.e., six times as many whites as negroes contract the disease. The death rate shows the same relative proportion between the two races. The number of return cases are also relatively less.

Heredity.—There is no evidence of heredity in the incidence of scarlet fever, but there is no doubt of the existence of a personal disposition to it. In rare instances such a disposition takes on a familial character. Welch and Schamberg report two personal observations of family epidemics and cite a number of instances from the literature. On the other hand, there is also a familial immunity to the disease.

Individual Susceptibility.—The individual susceptibility to scarlet fever, however, is not so general as for some of the other infectious diseases—variola and measles, for example. The classic instance of the epidemic of scarlet fever, in 1872, on the Faroë Islands, where no case of the disease had been known for sixty years, presented a favorable opportunity for estimating the general susceptibility to scarlet fever. In this practically virgin soil for the disease 78 per cent. of all the population developed scarlet fever, while in the same islands, in 1875, during an epidemic of measles, 99 per cent. of the population were affected.

Holt believes that not more than half the children exposed contract the disease. He quotes Billington's observation among families occupying tenements in New York, where little or no attempt was made to isolate the cases. Forty-three children were down with scarlet fever, while forty-six other children who had never had it and were constantly exposed to infection did not develop the disease.

Social Conditions.—As to social conditions, scarlet fever is not a class disease except in so far as crowded, unsanitary living conditions and poverty affect the predisposition to disease in general. Since the population subjected to such unfavorable environment is largely composed of the immigrant class, it is not surprising to find a proportionately greater incidence among the newcomers than among the native-born population or among the more prosperous classes.

The more intimate association of children housed in child-caring institutions naturally creates a favorable atmosphere for epidemics which, however, should and can easily be limited to such institutions.

Skin Lesions.—The rôle of skin lesions, especially burns, in the etiology of scarlet fever is practically the same as that of trauma in surgical and puerperal scarlet fever (*see* p. 254), where direct infection takes place through the open wound. That the broken epidermis undoubtedly serves as a favorable avenue for the invasion of the scarlatinal virus is amply demonstrated by the observation that the exanthem in such cases develops and spreads from the site of the wound.

(The association of scarlet fever with other acute infections is discussed on p. 251.)

EXCITING CAUSE.—*Bacteriology: The Organism.*—In spite of persistent and diligent research the specific incitor of scarlet fever has not yet been found. Since a full discussion of these investigations is not in place in a work of this kind, we shall confine ourselves to comparatively recent and more prominent studies of the question. With the discovery by Mallory (1904) of protozoön-like bodies in the skin layers of scarlet fever patients, it seemed as though the elusive agent was about to be definitely identified. Although the presence of these bodies was confirmed by many investigators, they did not prove specific. Döhle, in 1911, described certain bodies which he observed in the polymorphonuclear leukocytes of the blood from patients in the early stages of scarlet fever. These "inclusion bodies" he supposed to be in some way related to streptococcus infection. Their presence in the early stages is generally admitted. Kolmer found them in 94 per cent. of cases examined, but he also observed that after the sixth day their number decreased and they finally disappeared. But their specificity is questionable, since they are also present in the early stage of diphtheria as well as in other acute infections, such as erysipelas, puerperal sepsis, pneumonia.

The lack of animals suitable for experimentation has undoubtedly hampered the search for the scarlatinal organism. Up to the present time the monkey has been the only animal in which a disease resembling scarlatina has been obtained. Among the most recent experiments are those of Mair, who (1915) produced a scarlatiniform disease in the monkey from a diplococcus isolated from the throat of scarlet fever patients. The typical rash failed to appear, but the inclusion bodies were present in the polymorphonuclear leukocytes. This *Diplococcus scarlatinæ* was subsequently demonstrated by Mair in the first week of the disease in 87 per cent. (of 63 cases) of scarlet fever patients. The organism disappears, as a rule, about the fifth week of convalescence. It is at about this time in the disease that the patient first ceases to be infectious. Like the mysterious scarlatinal organism, the diplococcus produces profound toxemia which readily yields to the invasion of other cocci into the blood. There is as yet no evidence that the diplococcus enters the blood-stream in man to any appreciable extent; it appears to be confined to the region of primary invasion, i.e., usually the throat. Another striking feature of this experimental scarlet fever is that it is complicated by rheumatism; nephritis, however, is not as yet known to accompany the disease in the monkey. The absence of the typical rash does not necessarily exclude the possibility of the diplococcus as the causative agent of scarlet fever. Mair believes that when the actual factor becomes known this criterion of scarlet fever will undergo a change, since there is undoubtedly a much greater percentage of cases that fail to present the rash than is generally supposed. He also presents an interesting observation with regard to mice as scarlet fever carriers. When mice die as the result of being fed with cultures of the diplococci, or from the infection itself, the diplococcus is recovered from the blood. This applies also to wild mice, and may have an important bearing on the epidemiology of the disease, should the diplococcus prove to be specifically scarlatinal.

Mallory and Medlar (1916) have isolated a Gram-positive bacillus (*Bacillus scarlatinæ*) from the tissues of (two) patients dying of scarlet fever. This bacillus seems to be less virulent than the diphtheria bacillus but invades the same localities, and in severe cases may extend to the adjoining structures, especially the larynx, trachea and lungs. The toxin causes necrosis and destruction of the epithelial covering, thus leading to serous and polymorphonuclear exudates. The primary gross lesions are inconspicuous on account of the absence of fibrin and of membranous formation, except in cases of secondary streptococcic infection. In six instances, in smears from the tonsils and the soft palate, they obtained cultures of a bacillus whose morphology and staining reaction resembled that found postmortem in the tissues. After death, in severe uncomplicated cases, they found this agent in large numbers in the lesions in the respiratory tract; but in the milder ones it seems to die out quickly and is not easily demonstrated on the second or third day after the eruption appears. It may, however, persist for several weeks in the ulcerations in the tonsils, pharynx, larynx, esophagus, bronchi, so that patients harboring it may become scarlet fever carriers. At the same time the authors point out that the study of immune reactions was not positive; that the toxin could not be demonstrated from experiments with culture filtrates on human beings and on animals, although they believe "that it is entirely possible that the organism in tissues and smears has not been obtained in culture, as so far there is nothing but morphology to aid in its isolation."

Pryer and Sewell (1918) have isolated a large organism, with a tendency to be Gram-negative, from the blood of a fatal case of scarlet fever, which they believe deserves serious consideration as "a possible and probable cause of the disease." The organism seems to be the same as that described by Cantacuzène (1911), who isolated it from the throats of scarlet fever patients and, inoculating monkeys with it, produced a condition resembling scarlet fever. From cultures they prepared a substance which they call scarlatin (analogous to typhoidin from the typhoid bacillus), and using it as a skin test for immunity, found that it gave a higher percentage of reactions in scarlet fever convalescents than in other infectious diseases. They also observed that the probability of a positive reaction increases with the duration of the disease and in the absence of a history of scarlatina the probability of a positive reaction increases with the age of the person tested.

Streptococcus as the causative factor of scarlet fever has played a prominent part in the literature, but its actual rôle in the etiology of the infection remains to be demonstrated. As yet no specific scarlatinal streptococcus has been found, and to-day the streptococcus is generally considered to be a secondary infection. The importance of the streptococcus in the scarlatinal disease was observed as early as 1884, by Loeffler, who isolated it from the throat smears of anginose cases. His observations have been amply confirmed by numerous subsequent studies. The coccus is generally obtained from the throat in severe cases, but not all severe septic cases of scarlet fever develop a streptococcic infection. When, however, it is present it is characterized by marked persistence. Smillie observes the constant presence of a true hemolytic streptococcus in the severe cases of scarlet fever, but finds that the organism is less likely to be present in the milder ones, and that in many instances it persists in the throat for several months. He demonstrates the similarity of the particular strain of streptococcus ("beta" type) with that of septic sore throat, and believes that its persistence may be the means of transmitting scarlet fever as well as sore throat. Streptococci have also been found in the blood of scarlet fever patients. Moser observed them in 63 per cent. of cases after death, but Hektoen found them in only 12 per cent. of scarlet fever patients. Although they are frequently the cause of death, there is as yet no positive evidence that they are the cause of the disease. There is little doubt that the added virus of the streptococcic organism often dominates the picture and that the scarlatinal organism seems to create a special disposition (lowered resistance) to streptococcic infection. Kolmer illustrates this by finding a low streptococcus-opsonic index during the first week of the disease. He believes that the streptococcus of scarlet fever belongs to the general class of streptococci, but that it is modified in some way during the course of the disease so as to present certain specific antibody and transitory cultural characteristics. In fact, as already remarked, streptococci are not found in all cases of scarlet fever, severe or otherwise; the severe cases being often due to the overwhelming effect of the true scarlatinal virus without secondary streptococcic infection. Moreover, the injection of strains of scarlet fever streptococci in apes does not produce scarlet fever, although the blood of scarlet fever patients transmits the disease to animals (Landsteiner). Finally, the irregular results of antistreptococcic serum in the treatment of scarlet fever sustains the doubt as to the streptococcus as the cause of the disease.

The specific microörganism of scarlet fever, whatever it is, is generally conceded to reside principally in the upper respiratory tract, the discharges from which are the most fruitful source of contagion. The theory that the virus resides in the scarlatinal skin exfoliations has been entirely disproved by modern research. The virus is particularly tenacious of life and has been supposed to be the means of infection from *fomites* many years after having been in contact with a case of scarlet fever.

Modes of Conveyance.—The disease is communicable by *direct contact,* or through intermediaries, human beings, flies, insects and domestic animals, and by inanimate objects. There is also evidence of the milk supply as the apparent source of an outbreak of scarlet fever. But careful investigation will generally succeed in tracing the cause to the presence of the disease among the helpers or others connected with the dairy supplying the milk.

A not uncommon source of scarlet fever infection is the *carrier* of the disease who furnishes that most unwelcome type of case known as the "return case," which causes hospital authorities in particular no end of annoyance and unpleasant criticism, and which, unavoidable in a small percentage of cases, is so difficult to explain.

Every experienced physician has met with such return cases, the average of which is estimated at from two to four per cent. of all cases. A patient having recovered from a mild uncomplicated scarlet fever is sent home as clean, that is to say, all signs of desquamation have ceased, and there is no discharge from the nose, ears or throat. A week or two later some one in the family or in his environment develops a case of scarlet fever, apparently infected from the returned patient. When the original disease was accompanied by profuse rhinitis, otorrhea and suppurating glands this infectivity has been known to persist for several months after the development of the disease.

There is a tendency to hold hospitalization responsible for the phenomenon on the ground that the patients are sent home too early, or that if detained too long the atmosphere of a fever hospital is conducive to secondary infection, or that owing to carelessness in bathing the patient before dismissal, or lack of precaution during transference to the home, the patient catches cold and thus, through the medium of a catarrhal discharge from the nose, throat or ears, becomes a source of infection. If any of these were the true cause, the incidence of return cases would not be as comparatively low as it is. The question has received particularly careful attention from British physicians. It appears that not all the cases, so called, are actual return cases, that is, infection from recently discharged patients. Many of them are "incidentals" that develop at home after the incubation period from the first case has passed, either from lingering infection in fomites, or what is more likely, from unrecognized mild cases that have remained at home. This fact is often well demonstrated when a scarlet fever patient is ready to go home and, for some reason or other, is detained at the hospital. In the interim, say from two to four days, one of the members of the patient's family is brought to the hospital with the disease. If the recovered patient, instead of having been unavoidably detained, had been sent home, then this newcomer would naturally have been included in the list of return cases, whereas in reality he does not belong there. We are much inclined to agree with Arnold, who has studied the question from the standpoint of home conditions, and proves quite conclusively that the home conditions to which the majority of patients are returned have a preponderating influence on the incidence of return cases. In his very interesting study conducted at Manchester, England (1912), Arnold found that the greater number of cases of scarlet fever sent to hospitals for treatment come from homes that average more than one occupant per room and the average of susceptibles in such houses is twice as great as in homes where there is less than one person per room and where a scarlet fever patient is treated at home. This, together with the probably less intelligent and cautious after-care of a recovered scarlet fever patient (*see* p. 259) in such homes, should sufficiently explain the relatively greater incidence of "return cases" from fever hospitals as compared to "recovery cases," the term used by Arnold to describe the transmission of the disease by a recovered patient who has been treated at home. The question, therefore, to a large extent resolves itself into a social one, the solution of which is a matter of civic betterment, education and improved housing facilities. A certain proportion of these return cases being thus accounted for, it remains to explain the balance. In view of what we know of the persistence of scarlatinal infectivity, hospitalization is at fault only in so far as hospital construction and management are at fault. The ideal is, of course, to have separate rooms or small wards. Failing these, it is important to avoid overcrowding the wards. Then, also, the septic cases should be kept away from others, and should not be allowed to be sent out until all suppurations have ceased; or, in persistent cases, until a certain time limit has passed, which, of course, is arbitrary. We find a minimum of three months a good working rule for the release of patients with discharging nose and ears. There should also be separate wards for the acute cases and the convalescents, taking care, always, whether in the acute or in the convalescent stage, to keep the clean cases away from those that have discharging nose or ears. The patient should not be sent out immediately after a warm bath and, when ready to go home, should be dressed warmly and protected from draughts. The parent or guardian should receive very definite instructions as to after-care, such as prevention of cold, separation from others at home for at least two weeks, sleeping in a separate bed. With these hospital and home precautions carefully carried out, the percentage of return cases should be limited to those that are unavoidable, owing to the persistent infectivity exhibited by some patients, which, as Caiger puts it, should be considered as part of the natural history of the disease.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation.*—The incubation period of scarlet fever is not long compared with that of other infectious diseases. It may be as short as 24 hours; it is rarely longer than a week, the average time being from 2 to 4 days. But in considering the incubation period in this as in other infectious diseases, it is well to bear in mind the distinction between contact and inoculation and the variation in susceptibility displayed by different individuals. This aspect of the question is forcibly illustrated in a hospital for infectious diseases where the attendants are constantly subject to contact, but actual inoculation—the development of the disease—may take place in a few days, or may be delayed for several weeks, months or years, or it may never take place. For practical purposes, however, that is, for lifting a quarantine in a hospital ward or an institution and allowing exposed children to return to school, it is generally considered safe to regard 8 days (after the appearance of the last case, or after exposure) as the limit of incubation.

Mode of Onset.—A distinguishing feature of the disease is its sudden *onset* with practically no prodromal symptoms.

Symptoms during Progress of Disease.—A child, or an adult, in apparently normal health suddenly feels languid, complains of sore throat accompanied by vomiting, headache and fever, and in 12 to 48 hours—usually in 24 hours—presents the typical red rash and a flushing of the cheeks. The lips, in striking contrast to the pallor around the mouth, often appear redder than normal. The combination of intense angina and initial vomiting is so constant a feature of the disease that even in the absence of the exanthem it immediately suggests scarlet fever. The mucous membrane of the mouth, the pharynx and the nasopharynx shows a diffuse fiery-red eruption, that is, an enanthem is present as well as an exanthem. The site of greatest intensity of the enanthem is the *tonsils,* which in the severe cases appear markedly reddened and swollen and oftentimes are covered with a well-organized pseudomembrane, in many instances clinically indistinguishable from that of true diphtheria. The *nose* may show a profuse acrid discharge.

The *soft and the hard palate* present an uneven roughened appearance due to numerous reddened elevations or punctæ. These are of great diagnostic value in differentiating the angina of scarlet fever from other throat conditions, particularly in certain borderline cases of diphtheria. In institutions where diphtheria-scarlatina cross-infection is always a bugbear, these punctæ are especially worthy of study. They are also occasionally found in other than scarlatinal sore throat. Their absence, or rather, the presence of a pale, smooth palate is almost proof positive that the case in question is not one of scarlet fever.

The *tongue* presents a series of successive changes which are almost pathognomonic of scarlet fever and are of great diagnostic value. At first it is covered with a white furry coat through which the swollen red papillæ are seen to project. This so-called "white strawberry tongue" is often seen also in diphtheria and measles, but differs from the latter in that in scarlet fever the coating begins to desquamate in a day or two and by the fourth or fifth day it is red and glistening with the papillæ more or less distinctly prominent. Sometimes they are small and numerous, resembling the granulations in a wound; at other times they are scattered and more prominent. This "red strawberry or raspberry" tongue, or the fourth-day-and-after tongue, as it has been termed, persists for several days and is sometimes diagnostic as late as the seventh to the ninth day of the disease. After this the tongue gradually resumes it normal appearance. The consistency with which this desquamation takes place enables the experienced physician to tell almost at a glance and with almost invariable precision how long the disease has been present in a case seen after the initial period has passed.

The *submaxillary glands* are usually more or less enlarged, hard and painful; slight enlargement of the *postcervical glands* is sometimes observed, and generally the *inguinal glands* are also involved.

The *temperature* mounts rapidly, and in about 24 hours reaches its maximum—100°-103°-105° F. (37.7°-39.4°-40.6° C.), according to the severity of the case—at which it remains for the next two or three days, or as long as the eruption continues bright, and then falls by lysis, rarely by crisis. In the uncomplicated case this fall of temperature (by lysis) is one of the most constant features of the disease. Although a high temperature of 104° F. (40° C.) or more generally indicates a severe and possibly fatal infection, this is not necessarily so; such cases have been known to recover, while others succumb where the temperature curve was not unusually high.

The *pulse* is small, unduly tense and rapid, often more rapid than is warranted by the temperature, but without affecting the prognosis. In the more severe case the pulse is small, soft and obliterated at the arterial periphery.

Respiration is affected as in all febrile diseases.

The symptoms progress during the three, four or five days following onset, after which in the simple case they begin to abate. The rash begins to fade in the same order in which it appeared, from above downward, and desquamation then sets in. But the throat condition and the swelling of the tonsils and the glands, as well as the strawberry tongue, persists into the second week.

The *rash* begins on the upper chest and spreads rapidly upward, often covering the neck, going around in front of the ears to the temples, downward to the trunk, and lastly to the extremities, increasing in intensity during the first 24-72 hours after its appearance. It is often irritating and causes the patient to scratch the skin. The region around the mouth and the center of the face, in the majority of cases, is not affected and stands out pale and triangular—circumoral pallor—in marked contrast to the rest of the face. Other parts of the body not always affected by the rash are the scalp and the palms and soles, although the latter may be deeply flushed.

Under pressure from the fingers the eruption is obliterated, the underlying skin often appearing yellow (icterus) as the finger is withdrawn. Firm pressure with the fingers of the open hand will often show white lines that quickly disappear, but reappear with greater distinctness and remain visible for a longer time. Stroking the skin with the finger-nail will show either a white line (pallor) or a red line with a well-marked line of pallor on either side—secondary pallor. While of considerable aid in diagnosis, this secondary pallor can be accepted only as evidence, but not as proof, since a similar skin reaction often follows injections of diphtheria antitoxin or other sera.

In dark-skinned subjects, especially the negro, the eruption is often difficult to recognize. It may sometimes be seen by making strong pressure with the fingers on the soft parts (the upper arm or the abdomen), when it will be momentarily visible in the pallor resulting from the pressure. Oftentimes, on inspection, the palms and soles will reveal a red blush, and at the bend of the elbows, in the axillæ, the flanks and the inner aspect of the thighs a fine papular eruption will be seen.

The rash of scarlet fever varies greatly both in character and in distribution, probably more so than in any other of the eruptive fevers. It is best seen on the chest and the neck.

In the mild cases it is often evanescent and not infrequently is altogether wanting in certain parts of the body. Sometimes it begins to fade from the earlier affected parts before it has spread to the later ones, the extremities. In some severe cases also, especially where the throat symptoms are very pronounced, and in malignant cases, the rash may fail to develop.

The typical eruption appears in uniform bright red (or pink in the very mild cases) punctate spots, about half the size of an ordinary pinhead, on a more or less flushed background, although occasionally the skin between the points is normal. The skin is also sometimes swollen, especially when the rash is profuse. It may appear brighter on some parts of the body (the abdomen, and inner aspects of the thighs, the elbows, the axillæ) than on others, thus giving the body a blotched appearance. This irregular eruption is often papular and macular, as in measles. It is in these cases that it is visible on the palms and soles. This variation from the usual uniform punctation is also sometimes noted on the forearms and legs, where not infrequently the rash is definitely papular, especially about the shin—a valuable diagnostic point in cases that come under observation when the rash has already begun to fade. *Miliary vesicles* with turbid contents often develop, and not rarely the rash becomes petechial, especially in the creases of the skin, the hemorrhages being closely set and minute. These petechiæ often persist for some time after the eruption has faded from other parts of the body, giving a distinctly stained appearance to the skin.

The *desquamation* is even more typical of scarlet fever than the eruption, and often serves to establish diagnosis in the mild cases where the early symptoms have been indefinite. The process of shedding extends over a period of two or three weeks or more, continuing longest over the thicker parts of the epidermis, i.e., the soles and palms, always the last to clear up, and often falling off in casts from the fingers and toes. In fact, finger desquamation is pathognomonic of the disease. There is noticed at first a thickened, parchment-like feel of the balls of the fingers, accompanied or soon followed by a white line at the juncture of the pulp of the finger with the nail. The skin along this line may be separated with the physician's finger-nail and made to peel backward, coming off very easily in large strips or casts. This sign is of the utmost value in the diagnosis of cases coming under observation in the stage of convalescence.

Like the other manifestations of scarlet fever, the desquamation also shows considerable variation in character. It is often almost imperceptible, and affords no aid in diagnosis except in connection with the other symptoms. Often, too, it is present merely in the form of a powder which rubs off as the skin is being dried after a bath. This is especially the case in infants, but the powdery desquamation is also seen in older children at the anterior borders of the axillæ, at the lower part of the neck and between the fingers and the toes, and frequently as a little roughness on the shins.

The mechanism of the process is often described as a "pinhole" arrangement. The bursting of an inflamed skin papilla causes a breach in the skin, which at first small, increases in size and soon becomes visible as a pinhole in the cuticle; and as the process extends the increase in the size of the breaches in the epithelium and their coalescence cause flakes of greater or less size to become detached. The process is best seen on the neck and the chest and the outer aspects of the upper extremities.

LABORATORY FINDINGS.—*Blood.*—The blood in scarlet fever shows marked leukocytosis. The increase is supposed to begin during the incubation period and to progress with the course of the disease, ranging in the mild cases from 7,000 to 34,000, and in the severe ones from 14,000 to 40,000. The differential count shows mainly an increase, both absolute and relative, in the polymorphonuclears. Eosinophils, which at first are diminished, also increase toward the third and fourth days, a phenomenon which seems to be peculiar to scarlet fever and which might serve in differentiating it from tonsillitis and other septic infections.

Urine.—The urine is dark and scanty. The amount of urea excreted seems to run parallel with the fever, as much as four per cent. having been noted with a temperature of 103° F. (39.4° C.). Albumin is also present during the height of the fever. But this albuminuria is not generally considered to be related to the nephritis which is a feature of convalescence. The diazo-reaction is usually positive in the septic cases during the stage of eruption, and is sometimes regarded as a forerunner of a stormy course of the disease.

Diagnosis.—A diagnosis of scarlet fever would be justifiable when a patient gives a history of recent (within a week) exposure to infection, followed by a sudden onset of general malaise, sore throat and vomiting, the latter persisting in the severe case, but ceasing after two or three attacks in the mild case; the appearance, usually within twenty-four hours—sometimes later—of a diffuse red eruption beginning on the chest and spreading rapidly upward to the neck and downward over the entire trunk and the extremities; followed on about the eighth day—or later—by desquamation. In addition to these physical signs, the urine is dark and scant, shows slight albuminuria, and during the febrile stage, excess of urea excretion. The blood shows marked leukocytosis with marked eosinophilia during the early days of the disease.

The typical case thus is rather easy of recognition, but the symptom-complex is not always so clear. Oftentimes only a few of the above features may be present; at other times the picture is suggestive of disorders that are also associated with throat symptoms and the appearance of a rash, so that every practitioner at some time or other finds himself confronted with the question of differential diagnosis.

DIFFERENTIAL DIAGNOSIS.—In its very *early stage* scarlet fever may suggest a simple *tonsillitis, quinsy or influenza,* and occasionally *acute lobar pneumonia* may be mistaken for scarlet fever. But simple tonsillitis is rarely associated with initial vomiting, and the general disturbance is not apt to be very pronounced, while in quinsy the swelling in the throat is distinctly local, usually unilateral. There is rarely an eruption associated either with tonsillitis or with quinsy beyond a very rare, slight, non-punctate erythema on the arms, chest and back in tonsillitis, and an urticarial septic blotchy, also non-punctate rash on the elbows and knees in quinsy. But often the eruption of scarlatina anginosa is also blotchy and the punctations are indefinite. In such cases differentiation is not easy, and would rest on the absence of desquamation, a slower pulse and the presence of severe frontal headache. The absence of marked throat symptoms should help to distinguish influenza from scarlet fever. Unusually rapid respirations in connection with suspicions of scarlatina before the eruption has appeared should lead to an examination of the lungs before a positive diagnosis is made; but often the physical signs of a lobar pneumonia do not appear for several days. The appearance of the rash, however, should clinch the diagnosis.

In the *eruptive stage* the differentiation must be made from other acute exanthemata—measles, rubella, varicella, and the eruptions due to drugs, sera, sepsis, gastro-intestinal and other toxemias.

The confusion of *measles* with scarlatina often rests on a scarlatinal rash in the former and a multiform eruption, especially in the septic type, of the latter. On the other hand, occasionally in severe cases of scarlet fever there is a combination of morbilliform and scarlatinal rash (double eruption); should there be a concurrent coryza or conjunctivitis the difficulty of diagnosis would be enhanced. Again, in measles, at the beginning of defervescence the rash sometimes assumes the diffuse punctate character of a typical scarlatinal eruption. Differential diagnosis in such cases thus is a matter of circumspection and caution, especially where both types of eruption are simultaneously present.

Generally speaking, the differentiation can be made on the following basis: the incubation period of 10 or 12 days in measles compared to the 2 or 6 days of scarlet fever; the more diffuse and less punctate character of the rash which is preceded a day or two by the appearance of typical Koplik spots in the mouth; swelling of the face; the predilection of the rash for the face; absence of circumoral pallor. These, together with the spread of the rash behind the ears, distinguish measles from scarlet fever. The skin, after the acute stage is passed, shows a characteristic "coppery" or "mottling" pigmentation. As for desquamation, it is only the shedding of large scales that can be taken as positive evidence of scarlet fever.

The rash of *rubella* comes out in discrete spots, but often on about the third day, owing to coalescence of the individual maculæ, the eruption may resemble a real scarlatinal erythema from which it is scarcely distinguishable, indeed often absolutely indistinguishable. The throat symptoms, generally mild or absent, may be severe, even show a tonsillar exudate, and in some cases the fever may run high. But usually the fever is low and the pulse much less rapid compared to the temperature than in scarlet fever. Differentiation rests on the long incubation period (two or three weeks), the more evanescent character of the rash, the absence of tongue symptoms, as well as of circumoral pallor. Desquamation is unusual in rubella. The glandular enlargement differs from that of scarlet fever in being slight and usually painless; the glands are hard and discrete and sometimes cause a stiffness of the neck; involvement concerns the cervical, postcervical and in many cases the axillary and inguinal glands.

Varicella frequently presents a prodromal rash strongly resembling a scarlatinal eruption. The differentiation can usually be made on the mild onset, slight, if any, throat symptoms, the condition of the tongue and the absence of desquamation. However, the true varicella vesicles appear early, indeed, generally are the first signs of the disorder, and there is frequently the question to be considered of the simultaneous presence of the two diseases.

Variola also shows a prodromal scarlatinal rash, but this is rarely punctate and is more irregular and faint. Throat and tongue symptoms are not pronounced; backache is most marked and constant, and should help in differentiation. The irregularly distributed *erysipelatous* rash is hardly likely to be mistaken for the lobster rash frequently seen in scarlet fever, especially as in the former the face is uniformly puffy and congested in appearance.

Drug rashes are often caused by coal tar products, the salicylates, quinin, opiates and resinous substances, such as copaiba. The rash, however, is usually blotchy and well defined against the skin, compared to the gradually fading off of a scarlet fever rash. The most frequent cause of drug rash is the use of belladonna, whether given by mouth or in the form of a plaster or instilled into the eye for ophthalmic and other purposes. The eruption is erythematous, rarely punctate, and is followed by desquamation which may be powdery or may resemble the typical pinhole desquamation of scarlet fever. There is generally a transitory fever and delirium together with dryness and redness of the throat and more or less dilatation of the pupil; but the absence of tonsillar enlargement and of scarlatinal punctæ on the palate and of tongue symptoms, together with the history of the use of the drug, should serve to differentiate a drug rash from scarlatina.

The rashes due to *sepsis* and to foods causing gastro-intestinal and other *toxemias* may occasionally be scarlatiniform, but the absence of temperature and of throat symptoms, as well as the history of ingestion of certain foods—shell fish, strawberries, tomatoes, etc.—and of a personal idiosyncrasy, should remove any doubt as to the true nature of the eruption. Desquamation is also distinctive, usually beginning before the rash has entirely faded; it may be repeated several times at the same point and may include the hair, the finger-nails and the toe-nails. The skin after desquamation is brawny and red in contrast to the soft pink skin seen after scarlet fever desquamation.

Serum rashes of a scarlatiniform type are not unusual, and when occurring in the diphtheria ward of a hospital are a source of endless trouble; so much so that prompt and complete isolation of diphtheria patients presenting such a rash is imperative. The differentiation of serum rashes from the eruption of scarlet fever is discussed at page 158.

In the *desquamating stage*, differentiation must be made from other disorders such as rubella, serum rash, simple erythema, which are associated with more or less profuse shedding of the skin. The most reliable item is the history of the case which, if it include one or more of the usual complications of scarlatina, should decide in favor of the latter.

Complications and Sequelæ.—The complications of scarlet fever usually are troublesome, often stubborn, and not infrequently are the direct cause of death. Many of them are referable to aggravation or extension of the existing pathology which forms part of the symptom-complex of the disease, such as rhinitis, otitis, glossitis, scarlatinal rheumatism, etc. A strict classification into symptoms and complications is, therefore, not always practicable. Other complications appear late, during or after convalescence. These, then, may often with justice be considered sequelæ of the fever.

Of the early complications one of the most common, and probably the most intractable, is *rhinorrhea*. Destructive processes of the posterior nasal mucous membrane are manifested by a mucopurulent or a serous nasal discharge which is irritating and highly infectious and the persistence of which often delays convalescence and prolongs quarantine.

The infectious period, especially in young children, is also often unduly prolonged by *ear complications* which are said to take place in from 10 to 15 per cent. of scarlatina cases. The trouble may or may not be initiated with pain and fever and may vary from a trivial inflammation of the external canal, with possible involvement of the membrana tympani, and transitory deafness, to the more frequent manifestation of a typical otitis media, followed by a more or less profuse and persistent mucopurulent discharge. About 75 per cent. of severe cases of scarlet fever with pronounced throat and nose symptoms are said to be complicated by serious ear troubles. In the writer's experience, following conservative local treatment, this percentage has been markedly reduced.

The *aural complications* of scarlet fever may arise at any time from the fourth day to the third week, or later. *Otitis media* usually sets in during the third week but may also appear later. While infection may be carried by the blood stream, it is undoubtedly most often transmitted through the eustachian tube, and too often is the result of the pernicious practice of forcible syringing of the nasal passages.

The prognosis of otitis media is favorable, although in a percentage of cases, especially among young children, the suppurative process leads to *mastoid disease* often with superficial abscess formation. Mastoiditis is manifested by tenderness, swelling and redness behind the ear, and protrusion forward of the auricle which often stands out almost at a right angle to the head; also by fever and its accompanying symptoms. Sometimes there is a peculiar edema of the eyelid and over the zygoma on the affected side. Generally there is early evidence of pus formation beneath the periosteum; and at times exfoliation of bone. The condition yields rapidly to surgery.

Among unusual conditions due to an extension of otitis media may be mentioned *meningitis, cerebral abscess, thrombosis of the lateral sinus, pyemia and deafness,* the latter the result of irreparable injury to the middle-ear structures.

In rare instances collections of pus in the tonsils or sloughing of the throat in the anginose cases may lead to *retropharyngeal abscess.* This requires prompt drainage in order to avoid serious results—suffocation, septic pneumonia, generalized pyemia—from the pressure of the pus, or ulceration and possible rupture of a vessel from burrowing of the abscess.

Hemorrhage in scarlet fever, though rare, should be included among its complications. While exceptionally it may be due to hemorrhagic diathesis, it is more likely to result from extension of the necrotic process to one of the larger vessels. The hemorrhage may be arterial, venous or capillary, its frequency being in the order mentioned; it may also be arteriovenous. Erosion of one of the larger vessels is the most frequent cause of bleeding. The erosion may be large or small, with rough edges, and may vary in size from one millimeter in diameter to a sieve-like perforation. Hemorrhage from internal organs (liver, heart, spleen, stomach, lungs) may also take place, as well as from subcutaneous tissues with a more or less hemorrhagic pleural and pericardiac exudate. The outcome of this complication is usually death. Fatal otitic hemorrhage is very rare in scarlet fever. It has, however, been known to appear without any warning signs whatever, such as mastoiditis, facial paralysis or the like.

Synovitis scarlatinosa, or scarlatinal rheumatism, is a frequent complication of scarlet fever, occurring in about three per cent. of all cases, whether mild or severe. It may appear as early as the fourth day and as late as the third or fourth week, but usually sets in about the ninth day. The early cases are generally more severe than the late ones. It affects several joints at a time, preferably the smaller ones of the fingers, the wrist, ankles and knees, frequency being in the order mentioned; the vertebral joints may be, but seldom are, affected. In the severely septic cases of scarlet fever the affection of the joints may lead to *suppurative arthritis,* which, as a rule, attacks only one of the larger joints at a time—the elbow, or the knee. Occasionally the long bones become involved, with *periostitis* or *osteomyelitis* as the result.

The physical signs of *scarlatinal rheumatism* are pain, not so severe as in acute rheumatism, and swelling around the affected joints, swelling and redness of the overlying skin and dilatation of the superficial veins of the fingers and hand. Fever is nearly always present and generally lasts from five to seven days. There is very slight, if any, effusion into the joint cavity.

Symptoms of scarlatinal rheumatism may either precede or may follow the pyogenic manifestations of scarlet fever, such as otitis media, cervical adenitis, etc., and in rare instances may accompany endocarditis. Observations among soldiers in France during the world war show this association of rheumatism and endocarditis to occur in 27 per cent. of scarlet fever cases. This is no doubt largely due to trench life and other causes not active in civil life, since clinical observations among civilians show only a very small percentage of cases in which the two complications are associated.

The etiology of scarlatinal rheumatism is a matter of doubt which will probably not be cleared up until the true causative factor of scarlet fever is definitely determined. Its prognosis is altogether favorable. Any cases in which the symptoms persist for several weeks should arouse the suspicion of tuberculosis.

While myocardial inflammation is probably responsible for the extreme tachycardia often noted between the second and third week of scarlet fever, *heart complications* are, on the whole, uncommon. *Myocarditis* is manifested by a rapid, weak and sometimes irregular pulse with faint ventricular sounds, sometimes scarcely audible at the base.

Endocarditis occurs less frequently than myocarditis. Most of the cases reported as simple endocarditis, on careful study will be found to be due to cardiomyasthenia. Although the differentiation is not always easy, the presence of fever would indicate endocarditis, since myasthenia cordis rarely, if ever, presents a rise in temperature. In the endocarditis of scarlet fever there is generally mitral obstruction and insufficiency, but the aortic valve may also be involved.

Pericarditis, with a seropurulent or purulent effusion into the pericardial sac, may occur, but it is very rare and is usually fatal.

Pulmonary lesions also are unusual complications of scarlatina; severe cases are sometimes accompanied by bronchopneumonia, which may be a factor in causing death. Lobar pneumonia and bronchopneumonia may lead to pleurisy with serofibrinous effusion. Such effusions may also result from cardiac or pericardiac lesions, or in exceptional cases they may be tubercular. Mild types of pneumonia and bronchitis have been known to delay convalescence from scarlet fever during an epidemic of influenza.

Clinical observations seem to indicate a certain constancy in the time relation of the *later complications* and *sequelæ* of scarlet fever. Although they may arise at any time during or after desquamation, as late even as the seventh week of the primary disease, they generally make their appearance during the third or fourth week, the critical time being the 19th to the 22nd day. The most interesting of these later complications are lymphadenitis and nephritis.

Lymphadenitis, a glandular enlargement usually independent of faucial or other lesions, often follows a primarily mild case of scarlet fever. Its onset is sudden, marked by rise in temperature together with more or less pronounced glandular and periglandular swelling and tenderness; the trouble is generally unilateral, and affects the cervical and the submaxillary glands; sometimes both at the same time. The inguinal and axillary glands may also be affected. The acute symptoms usually subside in two or three days, but a subacute affection may persist for several weeks.

This lymphadenitis often is an important aid in diagnosis in limited epidemics in institutions and hospitals where only a few cases of scarlet fever develop, and some inmates have apparently escaped infection. The subsequent appearance of lymphadenitis among the latter would establish a diagnosis of previous scarlet fever, although the primary symptoms have been unobtrusive. These slight and aberrant cases are as capable as the severe and typical ones of undergoing the changes in the general condition which are responsible for the development of the complications and sequelæ of scarlet fever.

The prognosis of lymphadenitis is favorable. Even when accompanied by suppuration, recovery is prompt following free incision and drainage. Prognosis, however, is not so good when, as often happens, the adenitis is associated with nephritis.

Scarlatinal nephritis is justly regarded as the bugbear of scarlet fever. Its incidence depends on the severity of a given epidemic. On the average, it is supposed to complicate from 10 to 15 per cent. of all cases. Like lymphadenitis it seems to prefer the milder cases and is often the first sign of the previous existence of scarlet fever. This scarlatinal nephritis, as a rule, presents the clinical picture of acute hemorrhagic nephritis. Its onset is sudden, accompanied by a rise in temperature, vomiting, headache, loss of appetite, a feeling of fullness in the abdomen, but rarely abdominal pain. The face presents a peculiar pallor. Edematous swelling of the eyelids is sometimes the first symptom of nephritis. There is tenderness in the kidney region and occasionally a slight enlargement of the kidneys is palpable. The urine is scant in amount, dark, and in severe or advanced cases may be distinctly hemorrhagic in color. It contains albumin, blood, free red blood corpuscles and hyalin and granular casts. The specific gravity is increased and chlorids are diminished. The symptoms generally reach their climax in two or three days and subside gradually; they usually disappear at the end of two to four weeks, leaving perhaps a more or less persistent anemia. The renal disturbance in these favorable cases seems to have little effect on the heart, except for slight bradycardia, or a slow, tense pulse after defervescence, and increased blood-pressure.

Sometimes the symptoms of nephritis, albuminuria, for example, persist for many weeks, although the patient seems to be making favorable but slow progress toward recovery. This persistence indicates continued rest in bed, for it is only reasonable to assume that the pathological changes produced by the disease are healing slowly or perhaps incompletely, although functional derangement may have been sufficiently overcome as to present no great disturbance.

The great danger of nephritis, of course, is uremia, which often supervenes without any prodromal signs until convulsions set in. Sometimes, however, there may be headache, nausea or vomiting, loose stools, nocturnal unrest, slow pulse with increased tension, to indicate impending uremia. Some patients also show a peculiar staring expression or slight mental confusion just before the convulsive attacks appear. The temperature also rises after the appearance of the uremic symptoms, and represents the climax of the nephritis and dominates prognosis. In dragging cases of nephritis, if the patient is able to overcome the uremia, recovery finally takes place. But often death ensues either as the direct result of the toxic condition, or from complications caused by the same—pneumonia, pleuritis, cardiac weakness and a consequent pulmonary edema. The latter, in fact, is a more frequent cause of death than the uremic convulsions.

In spite of the aforementioned serious possibilities, the prognosis of postscarlatinal nephritis is, on the whole, favorable. Complete recovery, though it may be retarded for a year or more, is the rule in practically all cases, a fact confirmed by the most recent studies of this question.

Before leaving this subject of complications and sequelæ of scarlet fever it should be stated that literature contains numerous observations of pathological conditions accompanying or following scarlet fever which are claimed to be the direct result of the disease. We believe, however, that such observations are merely coincidences. Among such accidental associations may be mentioned appendicitis, peritonitis, diabetes mellitus, suprarenal lesions, sinusitis, hyperthyroidism, neuralgias and many others.

Relapses, Recurrences and Second Attacks of Scarlet Fever.—The distinction of these terms is often an arbitrary one, but it is usual to consider a relapse or recurrence as referring to cases in which a recrudescence of the disease appears either before convalescence has set in, or during convalescence, while a secondary attack denotes cases in which the patient experiences a true scarlet fever at a more or less remote period after recovery from the first attack.

Relapses or recurrences are unusual. Collected statistics show an incidence of 0.1-0.5 per cent. of all cases, the greater number occurring in fever hospital wards where constant addition of fresh cases keeps the air more or less surcharged with infection. A relapse or recurrence should be regarded as such only upon positive evidence of a primary attack. No indefinite symptoms should be accepted as indicating a true antecedent scarlet fever. Recurrences usually appear during the third or fourth week, generally around the 25th day. The symptoms are those of the original attack—vomiting, angina, fever, rash, desquamation—and may present the same peculiarities and variations. It is a general impression that the severity of the recurrence is in inverse ratio to that of the primary affection, that is, a light attack is likely to be followed by a severe one and vice versa. The prognosis, however, of the secondary illness is usually good, although death during such an attack has been reported.

The question is often raised whether these secondary attacks are instances of reinfection or of imperfect elimination of the primary infection. They are in all probability the latter, that is to say, incomplete immunization; for a patient cannot be considered as cured until immunization is complete and the disposition to scarlet fever is definitely overcome. Sometimes this immunity is delayed and the patient goes through more than one relapse. Welch has observed two recurrences in the same patient, eighteen and fifteen days respectively elapsing between the several attacks. Caiger reports a case which suffered three relapses within three months, the last one proving fatal.

Although one attack of scarlet fever is supposed to render the subject immune for life, this immunity may be lost later on and a *second attack* may take place at any time. Such second attacks have been observed by the writer at periods varying from six weeks to fifteen years after the first one.

Association with Other Diseases.—The association or coexistence of two or more infectious diseases is not unusual. Scarlet fever may be associated with diphtheria, measles, varicella, whooping-cough, mumps, erysipelas, variola, typhoid, in the order of frequency as enumerated.

Sometimes on the second or third day of the scarlatinal disease a rapidly spreading exudate develops on the tonsils and from there spreads to the entire throat, to the nose, the mouth, the eustachian tube, and may even involve the middle ear. This *membranous angina* was formerly known as scarlatinal diphtheria, but cultural studies have shown that it is not due to the diphtheria bacillus, but is of streptococcic origin.

The presence of the Klebs-Loeffler bacillus in cultures of such exudates would, of course, establish a diagnosis of *diphtheria* in conjunction with scarlet fever. The combination occurs much less frequently in private cases than in hospitals; but in modern institutions where culturing the throat effluvia of all scarlet fever patients is a routine measure, and where facilities are at hand for isolating and observing patients, the phenomenon has been considerably reduced in recent times. Postscarlatinal diphtheria is discussed on pages 140 and 148 of this volume.

The simultaneous appearance of the exanthemata of *measles* and scarlet fever is one of the puzzles of fever hospital management. A diagnosis of double infection based on the appearance of the rash alone should be made with caution. As has already been indicated, the rash in scarlet fever is often morbilliform, while in measles it may assume a punctate character on certain parts of the body. Sometimes the two rashes are simultaneously present. Diagnosis in such instances depends upon the development of symptoms pathognomonic of each of the two diseases—lacrimation, coryza, Koplik's spots for measles; scarlatinal angina, tongue symptoms and desquamation for scarlatina. There is no rule as to the priority of the two diseases. It is generally claimed, however, that prognosis is good when measles develops after scarlet fever, but not so good when scarlet fever follows measles.

The association of scarlet fever and *varicella* is not uncommon; in fact, it is said to be the most frequent combination of two acute exanthemata. When simultaneously present the probability is that varicella is the primary disease. Diagnosis, as a rule, presents no difficulty in view of the difference in character of the two eruptions; often it can be established on an enanthematous throat lesion—the typical varicella palate, or the scarlatinal angina.

Scarlet fever developing after a varicella eruption is well established is probably a case of mixed infection, a possible avenue for the second infection being a ruptured varicella or other skin lesion. The author has seen one such instance, and several have been reported by other observers. Scarlet fever following varicella is supposed to run a more benign course than does a varicella following scarlet fever.

As to the other infectious diseases mentioned, the symptoms may develop at any time during the course of the primary disease, but are supposed to set in more often when one or the other infection is beginning to subside.

The combination of simultaneous or concomitant infections is not limited to two; triple infections are not uncommon and quadruple ones not unknown. In fact, their number may be as many as the infections to which a given individual has been exposed, though they do not necessarily all appear during the acute stage of one or the other disease. We have seen scarlet fever combined with varicella and whooping-cough; with diphtheria and measles; with diphtheria, measles and epidemic cerebrospinal meningitis; also scarlet fever, diphtheria, varicella and whooping-cough; and scarlet fever, diphtheria, varicella and measles; with recovery.

Clinical Varieties.—While suddenness of onset distinguishes all cases of scarlet fever, the severity of the initial symptoms varies and usually corresponds to the severity to be expected in the subsequent course of the disease, which may be mild, moderately severe, or severe, the types being generally known as scarlatina simplex, scarlatina anginosa and scarlatina maligna. Other varieties are surgical scarlatina, puerperal scarlatina; some authorities also recognize a scarlatina sine exanthem as a clinical type of the fever.

SCARLATINA SIMPLEX.—In the *mild type*—scarlatina simplex—the symptoms, including the eruption, are often so vague as to cause little, if any, disturbance until the onset of complications or the beginning of the desquamation stage, which often too is slight, appearing as a fine white powder over the neck, the shoulders and the chest, at the tips of the fingers and between the fingers and the toes. Sometimes the typical rash is merely transient, unaccompanied by fever, while the throat is only moderately injected and swollen and gives scarcely any discomfort. Such cases may be missed altogether and remain undiagnosed until some one who has been in contact with the patient develops the disease in a more pronounced form or the patient himself experiences a subsequent attack of nephritis or other complications. For it should be remembered that these cases, in themselves so mild, are subject to the same complications—otitis, nephritis, etc.—and may be just as infectious as the severe types. They thus represent a serious menace and a fruitful source for the spread of the disease.

In the febrile cases of this mild type where the rash is less evanescent, the temperature, at first subnormal, rises to about 100°F. (37.7°C.), as the rash develops, and then on the second or third day falls to the normal and remains there.

In the *moderately severe* type all the symptoms are aggravated. The temperature rises quickly to 103° F. (39.4° C.), or more, the pulse is very rapid, the rash appears promptly, remains more or less intense for four or five days, when it begins to fade and usually disappears by the sixth or seventh day, by which time the fever also usually has subsided. The throat is redder than in the milder case, the tonsils, the uvula and fauces are involved, as are also the lymph glands at the angle of the jaw and the mouth, and swallowing becomes difficult. Small yellow patches often appear on the tonsils, but are not distinctly membranous and are easily wiped off. It is in these cases that serious ear trouble is apt to supervene. There may also be a seropurulent discharge from the nose, irritation from which excoriates the anterior nares and the upper lip. The inguinal glands are almost always involved, to some extent. During the height of the fever there is much thirst, restlessness and occasionally delirium. Though the patient is much prostrated and often anemic, barring complications, recovery usually takes place.

The *severe* forms of scarlet fever, as a rule, are ushered in with severe symptoms, and are usually divided into a septic type—scarlatina anginosa, and a toxic type—scarlatina maligna.

SCARLATINA ANGINOSA.—The throat condition is impressive and determines the seriousness of the case. The throat is patchy. Small flakes of exudate appear first on the tonsils, and as the disease progresses cover the tonsils and spread to the surrounding parts upward as far as the soft and the hard palate and downward into the larynx, in some rare instances causing a degree of obstruction requiring intubation.

The mucosa of the mouth is intensely congested and sometimes is the seat of ulcerations. Sordes develop on the teeth and lips, the latter becoming dry and cracked; ulcers of the aphthous variety show on the tongue, and fissures develop in the corners of the mouth.

The eruption is nearly always well developed. A frank eruption is most desirable, indicating good heart action; in fact, prognosis is unfavorable when the punctæ of an intense eruption are irregular in size and in distribution.

The severe symptoms persist from seven to fourteen days even though the eruption has begun to fade or has faded. The purulent discharge from the nose is profuse and irritating and is often transferred by the nails of the patient to other parts of the face, causing a local pustulous eczema. When the skin about the eyes becomes thus infected the result is a marked cellulitis, the swelling both in degree and color often suggesting erysipelas.

The enlargement of the cervical and submaxillary glands is marked, causing great discomfort, so that the patient makes no attempt to clear the throat and when compelled to swallow grasps his neck in trying to ease the pain caused by the act. There is also a typical tendency to throw the head back to relieve the pressure caused by the swelling.

This type of patient is very ill, and if a child is exceedingly irritable and restless, and very difficult to manage and to keep in bed. Delirium is marked, in fact, often wild enough to require restraint; dullness and apathy, as in typhoid fever, are exceptional. Anorexia is complete. This is the type of scarlatina that is frequently complicated by suppurating glands or discharging ears.

In some cases of this type of the disease the predominant symptoms are those of a general septic condition; oftentimes, too, they present a combination of throat symptoms with general sepsis. In rare instances the pharyngeal inflammation is gangrenous followed by sloughing which may expose or even open the large vessels, with fatal results.

Variations in temperature are often due to the development of one or the other of the complications that nearly always accompany the disease and frequently cause death after the patient has successfully thrown off the primary infection.

SCARLATINA MALIGNA.—Stormy onset and rapid development of severe toxic symptoms ending in death in a few (usually 12-24) hours characterize this fulminating, but fortunately rare, type of scarlet fever. Intense headache and cerebral symptoms, often with convulsions, usher in the attack, but the most prominent symptoms are diarrhea and persistent vomiting. The temperature rises rapidly, often going as high as 106° F. (41.1° C.), and even 108° or 110° F. (42.2° or 43.3° C.), and remaining high until the end or just before, when it may fall to subnormal. The pulse-rate not uncommonly is 160-170, with a soft, weak, irregular pulse, and feeble heart sounds. The urine is scant and albuminous.

The disease runs its fatal course so quickly that usually the rash hardly has time to develop; when it does make its appearance it is indistinct, scattered and dusky. The throat symptoms also are sometimes limited to a mere redness of the fauces, and there is often absence of glandular involvement. The patient is stuporous, with low muttering delirium; the cheeks are hollow, the eyes lusterless and oftentimes covered with a thin film. Just before death there is frequently a general lividity of the skin, especially on the trunk, which may take on a dark purple hue. Few patients survive beyond three days.

SURGICAL SCARLATINA—PUERPERAL SCARLATINA.—These are generally mentioned as clinical varieties of the disease, although there is much discussion as to the validity of the classification. Some authorities are inclined to regard them as cases of scarlet fever occurring in the wounded or in the parturient woman. Others feel justified in grouping them as cases presenting an atypical portal of entry of infection, through an open wound or through the genital organs, instead of through the pharynx.

SCARLATINA SINE EXANTHEM.—Scarlatina sine exanthem, if accepted as a clinical entity, well illustrates the fact that of all the infectious diseases there is perhaps none that shows so many deviations from the typical as does scarlet fever. The exanthem, as we have already stated, may fail to develop. The diagnosis in such cases is often made *ex post factum*, i.e., on the appearance of desquamation, the development of complications—adenitis, nephritis, with or without a history of an antecedent sore throat—or by the occurrence of a case of true scarlet fever in the family or in the environment of the patient. The fact that these cases show immunity when subsequently exposed to contagion is also offered as an argument in favor of including this among the clinical varieties of scarlet fever.

Treatment.—In the management of a communicable disease the physician finds himself in a most unique position, in that not a single but a three-fold duty confronts him, i.e., a duty to the patient, to the community in general, and to himself. The first concerns his professional skill in the matter of treatment; the other two concern the no less important question of prophylaxis.

The spread of infection is more easily controlled in those diseases for which the causative agent is known. In scarlet fever, therefore, the absence of such knowledge demands exaggerated rather than minimized prophylactic measures.

PROPHYLAXIS.—Isolation of the patient, of course, is imperative. Children and others who have been exposed to infection should be kept away from school and from other children or from contact with other individuals until the incubation period is safely passed. There is no objection to allowing the well children of the family to remain at home if the isolation and quarantine requirements are adequate and *are respected.* The father of the family or other breadwinners may be permitted to attend to business, provided it does not entail contact with children or young people, and provided, of course, that any proximity to the sick-room is conscientiously avoided.

The prophylactic use of **streptococcic bacterin** seems a rational measure, but here also the obscurity of the causative agent acts as an obstacle. The method has found favor in Russia since its introduction there by Gabritschewsky, in 1905. At the Philadelphia Hospital for Contagious Diseases the matter was tested in order to immunize diphtheria patients against outbreaks of scarlet fever in the diphtheria wards, and was found to be of little value.

According to the experience of Di Cristina, the desquamating scales of scarlet fever patients apparently contain an antibody which, if injected subcutaneously, seems to ensure immunity to scarlet fever. He was led to make the test, following the demonstration by Caronia (1914), of a specific antigen in the extract of desquamating scales of a scarlet fever patient and guinea-pig complement which induced the deviation of complement reaction. The test seemed to be positive in all stages of the disease, and served in differential diagnosis. Di Cristina thereupon prepared a vaccine of convalescent serum 15 c.c., desquamated shreds and scales 10 grams, to which were added phenol 0.8 per cent. and 1 c.c. guinea-pig complement, the whole being incubated for fifteen minutes at 37° C. (98.6° F.), centrifuged, put into vials and sealed. Ten children who had never had scarlet fever were given subcutaneous injections of

1 c.c. of the vaccine every second day; the deviation of complement reaction occurred after a second or third injection. The children were casually exposed to the disease and none developed it. A similar immunity was exhibited by some children who by mistake had been put into a scarlet fever ward of the hospital, inoculated twenty-four hours later, and allowed to remain in the ward. Di Cristina and Pastore now (1919) report forty successful instances of this prophylactic use of the vaccine. Children were allowed in the room with scarlet fever patients, even sleeping in the same beds with perfect immunity. The cases were followed up for six months, and the continued presence of the immunity was confirmed.

We give the above for what it is worth. We have had no experience with the method nor do we know of any tests that confirm Di Cristina's statements.

When scarlet fever develops in a school or institution the patient should be **isolated at once.** With careful observation of the other inmates and their examination at least twice daily by the public health authorities, and prompt isolation of all suspicious cases or close contacts, such as room-mates, it should not be necessary to close the school or institution, unless the disease threatens to assume epidemic proportions. To avoid this the facilities for such isolation should be of the very best, otherwise it is better to remove the patient to a fever hospital or to a private home, as the case may be. This question of providing for isolation and observation in schools and child-caring, as well as other institutions where young people are housed, is one of the most vital problems of public health administration. It is our conviction that no such organization should be granted a charter unless adequate arrangements for the complete and safe isolation of suspected cases are included in the plans of their building or buildings.

As to the precautions to be taken to prevent the spread of scarlet fever which develops in the ward of a general hospital or in a ward other than the scarlet fever ward of a hospital for contagious diseases, a full consideration of this question would not fall short of a complete discussion of hospital management and construction. In a general way it may be said that safety demands, of course, instant isolation of the patient. Next in importance is the separation from each other of all contacts until each one has safely passed the incubation period dating from the time the last case of the disease has been removed. This separation, to be effective in limiting the number of secondary cases that may arise, should be as complete as arrangements permit, use being made of every available room or side-room connected with the exposed ward. Or, in the absence of accommodations other than the ward itself, quarantine may be successfully managed, when the room is large, by keeping the children in different parts of the room, separated by screens. They should under no circumstances be allowed to mingle with each other. Their meals should be served to each separately. When using the toilet and bath they should go in one at a time. These patients should, in fact, be considered as occupying separate rooms, and no one in attendance should go from one to the other without changing cap and gown and washing the hands well with soap and water. These may seem like super-refined precautions, but fortunately, the incubation period of scarlet fever is short, and the extra trouble entailed is not great. It is worth while, if for no other reason, for the satisfaction of knowing that each patient has been accorded the fullest possible protection.

In modern fever hospitals with ample observation facilities such as obtain, for example, in the Philadelphia Hospital for Contagious Diseases, this plan of separating contacts can be carried out in an almost ideal manner, a separate room being provided for each person. Where this is not feasible the next best thing to do is to classify the contacts, placing the less susceptible with the more susceptible. For instance, it would be better to place a child with an adult than to put two children or two adults in the same room; or a young child under five—the more susceptible age—had better be placed with an older child over ten—the less susceptible age—than with a child its own age or younger; similarly it is better to have an acute patient with a convalescent than to have two acute patients together.

Sometimes in a general hospital the question arises of sending contacts home. At first such a proposition may seem hardly worthy of attention. But on consideration it has much in its favor, if the cases that are to be sent home are judiciously selected. By doing so we not only protect the exposed child or children whose vitality is already lowered by some disease or other, but at the same time we are reducing the chances of secondary cases arising by just so many as are sent home. In other words, not every contact in such a ward is infected at the first round, but he may get the infection from the second or third or any subsequent case that may develop. Sending him home removes that chance in a certain percentage of instances. On the other hand, if the contact has been incubating the disease and develops it in his own home, he would have developed it just the same in the ward of the hospital, where the chance of infecting already weakened children is much more of a menace. But, we repeat, the cases to be thus sent home must be very carefully selected with full regard to the type of case, the home surroundings and other details.

Measures less drastic than the foregoing have sometimes proved sufficient, such as merely disinfecting the bed of the patient who has been removed, and the adjoining beds or, as is sometimes done in European hospitals, treating the patient behind a closed screen, on the theory that infection is not air-borne. We mention these measures only to condemn them, since first of all, there is no positive evidence that infection is not carried in the air, and secondly, even if such evidence existed it is always better to err on the safe side, and surely so in scarlet fever, for which, of all contagious diseases, no half-way prophylactic measures are ever justifiable.

If the patient is to be treated in his own home, isolation should be as complete as circumstances permit. A most essential point and one that should be insisted upon whenever at all practicable is that the sickroom be provided with separate toilet facilities. The sickroom should be removed as far as possible from the rest of the house; the choice would be an entire floor at the top of the house. Where this is not feasible an ideal arrangement is that described by Griffith, consisting of the sickroom and an adjoining room which opens into a third room or hall, the windows in all three rooms being well screened, in order to prevent possible spread by flies and insects. Keeping the windows in the anteroom open as much as possible provides what amounts to an out-of-door passage between the sickroom and the rest of the house and prevents possible aërial convection. All the doors of the sickroom, except the one leading to this adjoining room, should be tightly closed and the cracks and key-holes stuffed with cotton or pasted over with strips of gummed paper, such as is used by disinfectors. The door of the anteroom communicating with the rest of the house should be kept closed when not in use for the purpose of exit or entrance. Hanging a sheet soaked in disinfectants (5 per cent. carbolic or 1/1000 sublimate solution) at this door is not of much, if any, protective value, but may be useful if for nothing else than to act as an ocular reminder that a quarantine is on and should be respected.

The furnishings of the anteroom should be limited to the most necessary articles, but they should by all means include a clothes-tree, washstand, bowl, soap, towels, etc.

The sickroom should be stripped of all unnecessary furniture, hangings, clothing, etc. Only such toys or books should be allowed to remain as are of negligible value and can be burned.

The attendant or nurse should wear a dress and cap of washable material. When leaving the patient she should change her clothing in the outer room, wash her hands well with soap and water, gargle her throat with **liquor antisepticus,** or some other mild disinfectant, and if going out, should leave the house without coming in contact with any of the family.

In this anteroom also the doctor, before entering the room, should remove his coat, put on a washable cap and gown, the latter to completely cover him. Wearing a mask is a wise precaution as a protection to himself and as a prevention against his becoming a possible carrier of the disease through the agency of his mucous membranes. After having seen the patient he should remove his protective outer garments in the anteroom, wipe off his shoes, disinfect and wash his hands well with soap and water, taking care to get the soap well under the finger-nails. All instruments which he has used, he will, of course, carefully sterilize. It is best to use wooden tongue depressors and applicators which, being inexpensive, can be burned. The doctor should endeavor to make this his last visit for the day, and in any case should again wash his hands before approaching the next patient.

The nurse should have her meals served in the anteroom rather than take them with the family. Her tray can be placed outside the sheeted door. Before taking it in she should wash her hands and put on a cap and gown. After she has finished her meal she can again set the dishes outside the sheeted door whence they can be removed and can with safety be washed in the kitchen. For her own protection she will not eat in the sickroom unless her constant presence there is imperative on account of the desperate condition of the patient—delirium, etc. In that case she should be provided with special utensils and dishes which she places outside the sheeted door and to which her food is transferred by a member of the household, great care being taken during the process of transference that her special dishes are not touched. After she has finished her meal she sterilizes and washes her dishes ready for the next meal. These same precautions also apply to the handling of the patient's food at all times.

The patient's bedclothes and his personal wear should be soaked for at least an hour in a disinfecting (carbolic or sublimate) solution, and after being wrung out of this can be thrown out of the window to be gathered up, or can be placed outside the anteroom door. They then can be safely washed with the household linen, if necessary.

Nothing should be allowed to be taken from the sickroom that has not been thoroughly disinfected. This applies particularly to excreta and any effluvia from the patient. For the nasal and other discharges, instead of handkerchiefs, pieces of gauze should be used, and these, as well as all soiled dressings, should be burned. In short, nothing from the infected zone should be placed in a clean zone, unless previously disinfected.

Instead of the carbolic solution which is expensive, Griffith suggests the following stock solution: carbolic acid (Calvert's No. 4), 6 fl. oz. (180 c.c.) and glycerin 4 fl. oz. (120 c.c.); adding 2.5 fl. oz. (75 c.c.) of this to water to make one quart (one liter) gives an approximate 5 per cent. solution.

After the patient has recovered and is ready to leave the room he should be given a cleansing bath, consisting of a generous soap and water lathering of his head and entire body; after this he is wrapped in a sterile sheet and taken into the anteroom, where he gets another soap and water bath. The throat and mouth should be cleansed with a bland mouth wash, such as Dobell's solution, as a gargle and retained in the mouth for several minutes; and after being dressed in clean clothes, the patient should be allowed to go.

In view of the uncertainty regarding the duration of the infectious period of scarlet fever, it is well not to allow the patient to sleep with any one for, at least, two months. It is best that kissing be dispensed with. If insisted upon it should be done on the forehead, but under no circumstances should the patient be kissed or kiss others on the mouth. He should be kept from other children for at least two weeks or as much longer as is convenient, and should spend as much time as possible in the open air. Especial care should be taken to guard a recently recovered scarlatina patient from exposure to draughts, chill, wet feet or any condition that may cause him to catch cold. The resulting discharge from the nose is apt to bring down germs that may be lurking in the many convenient hiding places in the nasopharynx.

This after-care of the patient is essential in every instance on account of its bearing on the vital question of preventing return cases (*see* p. 238).

It is here that the social worker, who should form part of the staff of every modern hospital, including fever hospitals, and the visiting nurse prove of inestimable value. A word of advice and an objective demonstration of the measures needed to safeguard the child and its associates are nearly always more effective than written instructions. The social service department recently established at the Philadelphia Hospital for Contagious Disease, although operating for only a short time, has already given ample demonstration of its worth.

After the patient has left the sickroom the latter should next receive attention. In our opinion all that is necessary is thorough cleansing with soap and water of the walls, furniture and other articles, although renovating the walls and refinishing the furniture add to the sense of security. The mattresses and pillows can be effectually sterilized by exposing them to the sun for several days. Subjecting them to a steaming process is of questionable value, but can be done if desirable.

Solely on the principle that the infectious agent of scarlet fever resides in the discharges from the nose, throat, ears and suppurating glands, and that in their transference lies the danger of disease-spread, prophylaxis naturally resolves itself into measures that prevent such transference, the mechanical means for which are direct contact, intermediaries—doctor and nurse, inanimate objects, air (in a limited sense), insects, domestic animals. As to the prophylactic technic to be observed we have here limited ourselves to the most essential features, but they are of the utmost importance in the performance of the aforementioned threefold duty of the physician. If rigorously carried out the danger of infection is reduced to a minimum; indeed, it is practically *nil.*

GENERAL MANAGEMENT.—The general management of the scarlet fever patient consists of **rest in bed** as nearly absolute as possible. Even in the mildest sort of case the patient should be kept in bed for at least four weeks in order to avoid exposure to draughts and sudden changes of temperature, thus reducing the risk of complications, such as nephritis, rhinitis, etc. In fact, it is better to keep the patient in bed during the entire course of the illness. The exception to this would be young children, not under the constant control of a nurse, who when not under supervision might get out of bed and suffer exposure. In such instances it is better to have the child dressed warmly and allow it to be up. Another exception would be on warm days when the patient, child or adult. could be wheeled out to a sunny porch.

The temperature of the sickroom is a matter of opinion. We find that the mild acute cases seem to do well at a room temperature of 68° to 70° F. (20° to 21.1° C.). But for the very severe case, especially the septic one with hyperpyrexia and delirium, a lower temperature is desirable—55° to 60° F. (12.8° to 15.5° C.), or even less when the air is dry, crisp and clear. The patient's bed should be kept as close to the window as possible and protected from draught by a screen (behind the bed) or sheets draped around the bed or crib, and the window kept open except in damp, stormy or blusterous weather. The patient should wear flannel bedclothes and have his head wrapped in heavy flannel or a blanket, leaving only the face exposed. Sometimes, as a protection against cold air circulating under the bed, an extra mattress as well as hot water bottles at the feet of the patient will be needed. The bed coverings should be warm but not heavy, fewer being required during the height of the fever than later on. With every precaution for keeping the patient warm the room temperature can, with advantage, be kept at less than 55° or 60° F. In fact, **fresh-air treatment** has everything in its favor. Where feasible this may even be interpreted to mean open-air treatment.

A daily sponge bath with tepid water and soap is essential. It adds not only to the comfort of the patient but assists in elimination and in restoring the skin to a normal, healthy condition.

Inunctions are of no curative value, but are useful in relieving the itching and preventing the scattering of the exfoliating skin.

Careful attention to obtaining a **daily bowel movement** and **ample urination** is of the utmost importance. For the former, **castor oil** may be given to children of four years or less; **magnesium sulphate** to older children or adults; or **pulvis glycyrrhizæ compositus** which is more pleasant to the taste. In addition to this the severe septic case with hyperpyrexia and delirium should have a **daily colonic irrigation,** preferably in the evening just before the patient is being prepared for the night. In the milder case and for all cases during convalescence an **enema** once a week is of advantage.

For the *kidney elimination* **free fluid intake** is essential. An average of one and one-half liters should be given (more or less according to age); adults, if they so desire, may have **carbonated waters.** If the fluid cannot be taken by mouth it should be given per rectum or in desperate cases by means of **intravenous injections of salt solution.** The daily output should be measured and a routine examination, microscopic and chemic, should be made at least twice a week or oftener if convenient or desirable. The information afforded by frequent urinary examination gives the doctor confidence as to the course of the disease and enables him to change or to increase the diet accordingly, especially where the patient rebels against the restricted régime in scarlet fever.

During the acute stage in severe cases it is well to bear in mind the possibility of *acidosis* as a contributing toxemia. For this reason **tests for acetone and diacetic acid** should be made when the patient's appearance—sunken listless eyes, sighing respiration, air hunger and restlessness—suggests the presence of acidosis. **Alkalis** are the indicated treatment, and it generally meets with prompt and satisfactory response.

Sleep is most essential, and on no account should the patient be disturbed for treatment, feeding or any other purpose.

The **diet** should receive careful attention at all times. During the vomiting stage of the disease it will do no harm to withhold all food.

After that a milk diet is an ideal one and should be adhered to, whenever possible. The average case can be kept on milk, as much as the patient will take, every three hours, and orange or other fresh fruit juice once a day until the temperature has been normal for seven to ten consecutive days. After this, if the kidneys are functioning well, both as to quantity and quality of output, the diet may gradually be increased to include cooked cereals, the pulp of stewed fruit, toast, bread and butter and light puddings. Very soon vegetables may be added, such as spinach, baked white potato, celery. Weak tea and coffee are permissible to those accustomed to their use. No further increase in the diet is advisable until after four weeks or until all danger from nephritis is passed. Sometimes, however, the severer cases with protracted fever, emaciation and weakness will require the low diet to be earlier supplemented by strengthening food; oftentimes this is followed by marked improvement.

In cases of persistent vomiting, **rectal feeding** may have to be resorted to and sometimes when the throat symptoms make swallowing difficult, **nasal feeding** will have to be tried. But this drastic measure is rarely necessary, for with tact and patience on the part of the nurse the difficulty may be momentarily overcome.

Little if any *medication* is required for the ordinary case of scarlet fever. The majority do well on rest in bed, sleep, fresh air, daily sponge bath, careful feeding, plenty of water, laxatives as needed and a bland mouth wash. Various drugs have been recommended, such as **biniodid of mercury, salicin, salvarsan,** but their efficacy has not been proven. The only medication we use as a routine measure during the febrile stage of scarlet fever is **citrate of potassium** given in large amounts of water every three hours, in full doses to adults, and 1 grain (0.065 gram) for every year of the child's age. After the temperature has been normal for four or five days **Basham's mixture** may be substituted for the potassium citrate. During convalescence, when the patient is on a more liberal diet, **syrup of iodid of iron, combined with syrup of hypophosphites,** is useful as a tonic; for marked wasting, **emulsion of codliver oil and malt** is beneficial.

Outside of the foregoing, medical treatment is purely symptomatic. We have already called attention to the desirability of a frank expression of the *rash,* since it indicates good heart action. In order to bring this about in cases where the rash is scant and ill-defined, the use of **hot-water bottles, hot packs,** or **wrapping the patient in heated blankets** is recommended. This can be done even though the temperature runs high, since the elimination that results helps to reduce the temperature and also diminishes the patient's restlessness.

For the *fever,* as long as the case appears to be a simple one and the temperature does not go above 102° F. (38.9° C.), an **ice cap** to the head (except for infants) is all sufficient. It also suffices where the temperature is 103° or 104° F. (39.5° or 40° C.), but is not accompanied by stupor, jactitation or other nervous symptoms. In the presence of the latter **hydrotherapy** is indicated. For this purpose we do not advocate cold, but prefer **warm water,** the choice being the **warm pack** repeatedly to gargle, it is well to use a solution of **normal saline or liquor antisepticus alkalinus,** N.F. Local treatment by irrigation, syringing or swabbing is strongly condemned except in certain conditions. For example, when the patient is an adult or a child old enough to coöperate, irrigation with normal saline as hot as can be borne may be allowed; or when ulceration takes place, it is permissible to use gentle applications of one-fourth strength **saturated solution of potassium chlorate** or **tincture of iodin,** twice daily, to the affected parts only. This, however, should be done only by an experienced person who is impressed with the necessity of extreme gentleness in the use of this measure. Better than this and much to be preferred is the use of a **spray** since it means less trauma from manipulation and less danger of introducing infection. A very valuable solution for this purpose consists of the following:

℞ Aq. hydrogenii peroxidi *	f ℥ v	(150.0 c.c.)
Ipecacuanhæ vini	f ʒ iii	(12.0 c.c.)
Glycerini	f ʒ v	(20.0 c.c.)
Aquæ	q.s. ad f ℥ viii	(240.0 c.c.)

For the *prevention of general sepsis* too much attention cannot be paid to the routine measure of keeping the mouth and nose, the portals of entry of infection, in an aseptic condition. Asepsis in this connection rests on cleanliness and the avoidance of irritation. The value of antiseptics is very questionable; if used they should be highly diluted, in order to prevent irritation to the delicate and already devitalized mucous membranes. Any skin lesions, such as burns or wounds, should also receive strict aseptic treatment, since they likewise present favorable avenues for the entrance and spread of infection.

The *mouth, gums and teeth* should be cleansed gently twice daily with a **cleansing, non-irritating solution,** such as Dobell's; or if preferred, a solution of either salt, or borax, or bicarbonate of soda, alone or combined with 10-20 per cent. glycerin, may be used. In case of *mucous membrane infection* which is apt to occur in mouth-breathers, the cleansing of the mouth should be followed by some **oily solution,** such as liquid albolene, to allay or prevent irritation to the delicate mucosa. The condition of the *teeth* is of vital importance. Whatever can be done during the course of the scarlatina to remedy defects, such as collections of tartar, carious teeth, etc., should be done, for the teeth as a persistent source of infection is to-day a matter of common knowledge. All **necessary dental work should be attended to** before the patient is discharged from the hospital.

The *asepsis of the nose* is just as important as that of the mouth but often presents some difficulty, especially when infection extends to the nasal vault and the nasal sinuses. Forcible syringing is absolutely contra-indicated, as it is apt to spread infection. **Gentle mechanical cleansing** with a swab is permissible. If the patient is able to blow the nose he should be encouraged to do so; **ointments and medicated oils are**

---

* Aq. hydrogenii dioxidi.

recommended for their protective and mild antiseptic value. In certain cases where the nasal discharge is profuse and the patient is stuporous or otherwise unable to coöperate, we have kept the nose open by means of a syringe and catheter.

Enlarged tonsils and adenoids also often act as sources of persistent infection. Their **removal** as early as possible in the acute stage is advocated by some authorities and is said to have proven beneficial.

The **routine inspection and treatment of the nose, mouth and throat** are essential also, because they permit early recognition and prompt attention to *complications* that may occur, such as rhinorrhea, tonsillitis, diphtheria, measles (Koplik's spots) and other rare conditions, such as abscess, peritonsillar or retropharyngeal. For, in spite of the most careful management, complications in scarlet fever can often not be avoided. These should be treated as they arise.

For the *cracking of the lips*, which though not serious, is troublesome, **compresses of camphor water** or of the preparation of **hydrogen peroxid, glycerin, wine of ipecac and water,** mentioned on page 264, are, in our experience, more efficacious than ointments. It may sometimes be necessary to put the **child's arms in splints** in order to prevent picking and consequent infection of the lips.

For the *aphthous stomatitis* which often appears on and under the tongue in cases in which, for some unaccountable reason, the temperature remains around 100° to 101° F. (37.8° to 38.3° C.) the **same solution may be used as recommended for the throat. Spraying the extruded tongue** is the most convenient way of treating such sores.

Rhinorrhea, one of the most intractable complications of scarlet fever, is best treated conservatively. Encouraging the patient to blow the nose is better than irrigation. Instillations of 15 per cent. **argyrol,** we have tried with indifferent success. **Insufflations of calomel** are also recommended by some physicians. In order *to facilitate drainage* we have found it advantageous to use the following solution:

℞

Menthol	grains ii (0.13 gram)
Iodi	grain i (.065 gram)
Camphoræ	grains iii (0.20 gram)
Eucalyptol	f ʒ ss (2.0 c.c.)
Liq. albolene	q.s. ad f ℥ i (30.0 c.c.)

M. et S.: Five drops to be instilled into each nostril three times daily.

It is when rhinorrhea persists past the fifth week, in otherwise uncomplicated cases, and renders the patient a most probable carrier, that the **excision of adenoids or enlarged tonsils** is called for, and will in most instances result in a cure.

For the *eye complications*—conjunctivitis, blepharitis, ulcerative keratitis, the latter the only one that may prove serious—the treatment is the same as when these arise in other conditions.

In the rare instances in which membranous or ulcerative laryngitis occurs intubation or tracheotomy may have to be resorted to. The differentiation of these cases from diphthèria is discussed on pp. 140, 251.

Serious ear complications can often be avoided by conservative treatment of throat and nose troubles (*see* p. 264). We mention only to condemn such practices as **nasal irrigation, palpation of the nasal vault for adenoids, forcible washing of the throat, faulty (Trendelenburg) position,** etc. *Acute swelling and obstruction in the nose* can be prevented by **instillations** of the solution mentioned above. Sometimes **inhalations of 1/8000 adrenalin** may be of service. But in spite of all precautions otitis media may arise, very often owing to the presence of adenoids or large turbinates which act as contributing factors. The treatment of the nose and nasopharynx has been indicated above. In addition to this, any *perceptible bulging of the drum membrane* demands **immediate free incision** which may and should be repeated as often as required to maintain free drainage. As long as the drainage is sufficiently free nothing more will be necessary, for this generally relieves the condition with no further treatment except external cleansing and keeping the canal free. Any additional local treatment, should it be found desirable, should be applied only by the doctor in attendance or by a specialist, and never without the aid of the head-mirror and the speculum.

We do not advise **irrigation** except where the discharge is thick and interferes with free drainage. In such an event **irrigations of warm boric acid or saline solution** 100°-105° F. (37.8°-40.6° C.) may be used as often as required in a given case. For a thin discharge Place suggests the following **dry treatment** instead of irrigation: The ear is frequently sponged with sterile cotton and a narrow wick kept to the drum, but not so as to fill the canal closely, and supplemented, if desired, by insufflations or instillations of 5 per cent. boric acid in 15 per cent. alcohol solution.

It is only by the **early treatment of ear symptoms** that the more serious complication of mastoiditis can possibly be forestalled. Should it develop, the prompt application of **external heat** (hot-water bag) and vigorous attention to obtaining **free drainage** may sometimes avoid operation. The use of **ice-bags** is advocated by some practitioners. This, however, is indicated only at the very inception of mastoiditis, and as the exact time of that stage is most uncertain, we feel it is safer to dispense altogether with the use of cold applications.

A marked redness, swelling or tenderness behind the ear together with indications of systemic disturbance, high temperature, etc., that persist for more than 48 to 72 hours, demands operation—**excision of the mastoid cells**—at this stage. Any more radical surgery that may be required, owing to a chronic condition developing, should be deferred until after the purely scarlatinal symptoms have disappeared, and then should be done by a competent surgeon.

Much of the general management of scarlet fever is directed toward *avoiding postscarlatinal nephritis.* In this connection it may be observed that in a large series of cases we studied the blood-pressure, in the hope that it would afford some warning of an incipient nephritis, but the results did not fulfill our expectations. In spite of all precautions nephritis will develop in about 10 per cent. of the cases, although the incidence varies with the severity of a given epidemic. When it occurs it should be combated by energetic and vigorous measures. The patient, if he has been out of bed, should be immediately **put back and kept in bed** for at least three weeks. The **diet should again be rigidly limited** to milk and free intake of water. Later on, when the ravages of the disease have caused emaciation and anemia, although the urine may not yet be altogether free from albumin, the diet should be increased by the addition of foods of low protein content, that is, chiefly carbohydrates and fats (to be served with little or no salt), such as green vegetables (except asparagus), bread and unsalted butter, stewed fruits, cereals, light puddings. Sugar should be freely given. There seems little doubt but that the withdrawal of salt from the diet acts favorably in reducing any dropsical swelling. It is natural therefore to assume that a salt free diet should also aid in preventing the development of edema.

The bowels should be kept freely open. For this purpose we generally use for adults and older children, **magnesium sulphate or pulvis jalapæ compositus,** and for children of four years or less, **oleum ricini.**

As long as *diuresis* is satisfactory **free intake of fluids**—water, lemonade and mineral waters of low salt content—**is advisable.** A palatable substitute for lemonade and one that is cheap and easily made is the Imperial Drink used in England. It consists of potassium bitartrate, 2 drams (8 grams), sugar, 1 oz. (31 grams), the juice of one lemon, added to one quart (1 liter) of boiling water, thoroughly mixed. This, diluted to taste, can be placed at the bedside of the patient for him to take at will, not alone for any specific action of the drink itself, but with the idea of encouraging the free intake of fluid.

With the appearance of *oliguria* (500 c.c. urine in 24 hours) the **fluid intake should be somewhat restricted.** For *diuretic purposes* we recommend the routine administration of **potassium citrate and ammonium acetate solution.** Later on these may be substituted by **Basham's mixture.**

Diaphoresis, especially when the amount of urine is reduced, is of the utmost value because it produces free elimination and thus helps to lift the burden from the crippled kidneys. It can be employed in the form of a **hot wet pack, vapor baths or electric light baths** and, according to the exigencies of the case, at intervals of every four hours to once daily, repeated until the urine has been found negative on four consecutive days. After this it may be gradually discontinued and the **diet** correspondingly increased.

The *hot pack* can be given as follows: Protect the bed with a rubber sheet or a cotton quilt folded. Two folded sheets are then wrung out of hot water, several degrees hotter than desired for the application, one of the sheets is laid on the bed and the patient is placed on it, the other one being used to cover him, care being taken that it comes in contact with all the skin surfaces, especially in the kidney region. The arms should be wrapped in towels wrung out of hot water, and the pack covered with heated blankets or a quilt. From twenty to forty minutes is the average time for keeping the patient in a hot pack.

The *vapor bath* can be given by heating water over an alcohol lamp under the bed, and conducting the steam through rubber tubing placed between the covers of the bed.

In our opinion the most practical form for giving these sweats is the electric bath. It is less depressing, less liable to produce burns, and more easily arranged with less exposure of the patient. A practical apparatus is one devised by Tracey, consisting of a frame or cradle covered with asbestos and provided on the inside with six or eight electric light bulbs connected by a long cord which can be attached to any electric light socket. The frame fits over the patient's body, and when in use is covered at both ends to keep the heat in. The heat can be regulated by turning on the lights and reducing the number used in case it becomes too great.

To-day when even the smallest village is lighted by electricity this method of sweating is often much easier to procure than a large amount of hot water and all the paraphernalia for giving a hot pack or a vapor bath. The apparatus is simple and portable and can easily be included in the armamentarium of the physician.

With the proper vigilance and conscientious study of the case on the part of the physician, neither edema nor uremia should develop in a case of scarlatinal nephritis. In some rare instances, however, in spite of all precautions—including frequent and careful urinalysis—these undesirable phenomena may supervene. In such an event *edema* can generally be controlled by **reducing the liquid intake, withdrawing salt entirely from the food, providing for free watery catharsis,** and **administering diuretics, potassium citrate or ammonium acetate solution.** If both of these are used in the same case they should be given alternately every two hours. Active counterirritation with **dry cupping** followed by **poultices of mustard and flaxseed** in the proportion of 16 to 1 will be useful. The poultice should be applied as hot as possible and should be large enough to cover the entire kidney region.

Symptoms of uremia or of impending uremia, such as mental apathy, drowsiness or coma, headache, delirium, muscular twitchings, disturbance of vision, marked reduction in urinary output, convulsions, require **energetic and quick action.** If convulsions set in, prompt measures are demanded for their control and to prevent their recurrence. The patient should immediately be placed in a **hot pack or a warm bath,** 104° F. (40° C.). **Offering chloroform for inhalation** in small whiffs helps to relax the patient. **Venesection** is important for reducing the blood-pressure and should be resorted to as promptly as possible. It may or may not be followed by **intravenous injections of salt solution,** opinions being divided as to the necessity for the latter. We find that most patients do well without it. The **blood** can be taken from the arm of the patient either by **incision or by aspiration,** about 100-200 c.c. being withdrawn from a child up to ten years, or 300 c.c. for an older child or an adult. This generally gives temporary relief and also gives time for other measures, such as **diaphoresis** and **purgation,** to act. Vomiting can be controlled by allowing the patient to swallow **small pieces of ice. Colonic irrigation** with a quart (one liter) of hot water assists in eliminating toxins and prepares the bowel for rectal medication, such as chloral or chloral and bromide. If there is any doubt as to the *free action* of the *bowels,* a **hydragogue cathartic** should be given, such as magnesium sulphate or elaterium for adults, and in desperate cases also for children. This can be administered through the nose by means of a catheter, if the patient is unconscious. We have tried **lumbar puncture followed by injection of a solution of magnesium sulphate in sterile water,** as is done in tetanus, but the results have not proven of any great value.

When the patient revives, it is essential that he be kept very warm, by the measures already indicated. The treatment then is that of acute nephritis. *As improvement sets in*—as evidenced by increased urinary output and reduction of albuminuria—the **heat of the bed can be gradually reduced** and the **diet cautiously increased.**

The *cervical adenitis* that accompanies a mild case of scarlet fever requires no treatment, since it usually subsides with the acute symptoms. For the more pronounced cases various remedies have been recommended, such as **ichthyol, methylsalicylate, iodin petrogen, colloidal silver,** but their efficacy is doubtful. **Cold applications** may be helpful, but as in mastoiditis, only in the very early stage. If used, great care should be taken that the ice-bag fits snugly around the affected parts and does not rest on the chest, as so often happens. We at all times prefer **heat,** either by the water-bag or the electric pads, or fomentations. In our experience heat does not favor suppuration; in the milder cases it promotes resolution, while in those that would break down under any treatment, the process is hastened. When the process is complete—but not until then—an incision in the fold of the neck should be made. The incision should be fairly free in order to insure prompt healing with a minimum degree of scar. When the destruction of the gland has once begun it must go on to completion, and **too early incision** would prolong the process and also afford opportunity for secondary infection.

The *cervical cellulitis* that develops in the severe anginose cases is best treated with **hot fomentations.** Early incision will not prevent sloughing of the skin and the subcutaneous cellular tissues; it is best therefore to wait until the skin has softened, or according to some authorities, until it has broken down. The underlying slough should be removed with great care, and any particles that may not have separated from the healthy tissues should be allowed to come away of themselves, since force of any kind is apt to induce troublesome hemorrhage. After incision, the **wound should be treated on the usual surgical principles.** Only the blandest solutions, such as saline or boracic acid, should be employed. **Irritating solutions and packing** tend to aggravate the process of sloughing and reduce the chance of recovery which in these cases, at best, is unfavorable.

nign than formerly is universally recognized. This is to some extent due to the more general custom of sending scarlet fever patients to hospitals, where, as a rule, they can receive better care than in the average private home from which the cases come, and partly also to the growing practice of administering diphtheria antitoxin to scarlet fever patients, inasmuch as the combination of the two diseases yields very high mortality figures.

The influence of *sex* on mortality is unimportant, although the death rate seems to be somewhat higher among males of all ages than among females. Infants, though rarely affected, show a relatively higher death rate than older children; the highest mortality figures occur during the first five years of life, but for children of all ages 90 per cent. of deaths from scarlet fever occur among those under ten years of age. The colored child has a better chance of recovering from scarlet fever than has the white child. Dublin gives a relative mortality of four to one among white and colored children respectively. We find the death rate to be six times greater for the white children than for the colored ones.

As to *functional results,* except for the rare instances in which severe, and probably improperly treated, ear complications result in impairment or loss of hearing, there are no indications that scarlet fever—unlike typhoid fever—once overcome, leads to any permanent functional derangement or to a particular susceptibility to other infections, such as tuberculosis, etc.

Pathology.—The gross lesions of scarlet fever are few and much slighter than might be expected from the oftentimes severe character of the clinical features. The principal ones are a more or less marked acute dermatitis, and a catarrhal or inflammatory process of the mucous membrane of the mouth and throat. This process is seldom gangrenous or necrotic, and occurs only in the anginose and diphtheroid cases. It rarely involves the larynx. It, however, often extends to the middle ear and the nose; from the former it may spread to the mastoids, the meninges, the brain; and from the latter to the accessory sinuses, especially the antrum of Highmore. Congestion may also extend to the esophagus, while involvement of the cervical lymph glands and the surrounding tissue may lead to cell hyperplasia, suppuration and gangrene.

The skin eruption, which sometimes covers the mucous membrane of the mouth and throat, is not seen after death. The one constant feature which is found at autopsy in all cases of scarlet fever is hyperplasia of all the lymphoid tissues. Other important lesions, due mainly to complications of the disease, are degeneration of the parenchymatous organs, the liver, the kidney, and, to a less degree, the muscles of the heart, which often is dilated and hypertrophied as a result both of the scarlatinal poison and the kidney involvement. In the severely toxic cases with wild delirium there is edema of the brain and evidence of meningeal inflammation; splenic tumor is also sometimes seen. In these severe cases the rapidly fatal course is no doubt due to the overwhelming toxicity of the causative agent of the disease, although other contributing factors, such as status lymphaticus, are often noted postmortem.

Circulatory System.—The *changes in the heart* are mainly a fatty degeneration of the muscles. Recent studies, however, have shown marked pathological changes in the heart ganglia, to which the cardiac paralysis in the severely toxic and rapidly fatal cases is attributed. In a special study of the myocardium and the heart ganglia in scarlet fever, Stegeman found round-cell infiltration in the stroma of the heart ganglia constantly present, even from the first day of the disease, its intensity being dependent on the severity (complications) and duration of the illness. Fatty degeneration and necrosis of the nerve-cells are likewise present from the first day of the scarlatina. Nissl bodies, in the severely toxic cases with early death, were markedly diminished in size and number when compared to the more prolonged cases. In the latter (septic and pyemic cases), where death ensued after the fifth and up to the thirty-eighth day, the myocardium showed parenchymatous and fatty degeneration as well as necrosis.

According to the studies of Klein and of Pearce (cited by Welch and Schamberg), the *changes in the lymphatic glands* consist of hyaline degeneration in the center of the gland in which are found large cells, some resembling giant cells and others having transparent vesicular nuclei. The sinuses are dilated and contain many endothelial cells lying free in the lumina, as well as large and small cells with one or more transparent nuclei, some of the cells showing phagocytic properties. The blood-vessels are congested, occasionally showing signs of hemorrhage.

In the severely toxic form of scarlet fever in which the necrotic process in the nasopharyngeal region is the dominant feature, the streptococcus is recovered from the tissues as well as from cultures of the accumulations in the mucous membrane, the submucous tissues and the regional lymph glands. It is conceivable that the organism not only sends its toxic products from the throat into the blood stream, but that it may also penetrate the vessels and from these enter all other organs which not infrequently develop pyemic processes in which pure cultures of streptococci are found to reside, and which add to the pathology of scarlet fever. Such conditions comprise multiple joint suppurations, abscesses of the peri-articular tissues, muscle abscesses, subcutaneous abscess formation, purulent disease of the serous coatings (pericarditis, endocarditis, peritonitis), etc., all of which have been considered under complications of scarlet fever.

Pearce, to whom we owe much of our knowledge of the morbid anatomy of scarlet fever, describes the changes in the *tongue* as dilatation of the papillary blood-vessels and lymphatics and leukocytic infiltration of the epithelial layers, especially over the papillæ and among the blood-vessels. He regards the process as an inflammatory one, probably due to positive chemotaxis excited by the scarlet fever toxin present in the tissues or by the products of its action on the superficial epithelium.

Respiratory System.—The lesions of the pulmonary region, in the cases where it is involved in scarlet fever, are usually those of a bronchopneumonia affecting one or both sides. That they are due to the scarlatinal infection is seen from the presence of streptococcus associated with staphylococcus aureus. The pleura likewise may be attacked by the streptococcic infection; the route of infection from the respiratory passages to the pleura has been traced by Simonin by areas of hepatization of the tissues.

Digestive System.—*Gastro-intestinal Tract.*—Involvement of the gastro-intestinal tract is not one of the features of scarlet fever, although in rare instances the necrotic process from the throat has been known to extend along the esophagus and into the stomach, causing more or less pronounced destruction of the mucous membrane along its route. Involvement of the intestinal mucosa is usually limited to catarrhal enteritis.

Liver.—Hepatic enlargement is one of the most constant gross findings in scarlet fever. The icteric discoloration of the skin and the urobilinuria, often seen at the height of the exanthem, are undoubtedly due to disturbed liver function. Histological studies demonstrate a constant, more or less marked small-cell infiltration of the connective tissue extending to the parenchyma, and in some rare instances, necrosis. The latter may, however, undergo regeneration. Interstitial hepatitis, lymphatic neoplasms and cirrhosis have also been observed.

Spleen.—The changes in the spleen are generally described as consisting either of enlargement of the splenic pulp or enlargement of the malpighian bodies without increase in the size of the pulp, which in such instances has a firm, smooth but not tense capsule. The malpighian bodies appear as prominent grayish-white areas against a dark, reddish background. When the pulp is enlarged it is soft, and the malpighian bodies are indistinct. In stained microscopic sections their centers are pale, while the periphery is deeply stained and contains many plasma cells. This infiltration of plasma is also observed in all parts of the pulp within the blood-vessels and along the trabeculæ. The center of the malpighian bodies consists of more or less fused phagocytic cells—masses of endothelial cells from the lymph nodules.

Urinary System.—The kidneys, of course, occupy a very important place in the pathology of scarlet fever. The anatomical changes in scarlatinal kidney disease are those of an interstitial and a glomerular nephritis. In the former the kidneys are more or less swollen and their superficial surfaces dotted with red spots; in cross section a striated redness of the dilated cortex is seen, the markings of which are ordinarily obscured. Microscopically there is an accumulation of lymphocytes, the density of which has a direct bearing on the degree of leukocytic infiltration and consequent structural destruction. These changes may be present early in the scarlet fever, especially in the septic cases, without producing any clinical manifestations, but when they are diffuse the symptoms are correspondingly intense, and in cases where the entire kidney is affected death may ensue. The glomeruli themselves remain intact. In fact, nephritic foci may persist beyond the third week of scarlet fever and clinically present no symptoms of nephritis without glomerular involvement. Escherick and Schick suggest that the cases so often reported of slight clinical symptoms and marked renal changes probably belong to this class.

In the glomerular nephritis, generally regarded as typical of scarlatinal nephritis, the kidneys, except for a slight edema, appear normal at a first glance. It is only upon careful examination that the glomeruli are seen on the cut surface, to which they lend a granular appearance. All the granules are affected, but other changes may be slight and unimportant or altogether absent.

The first visible signs of pathological changes are thickening of the walls and increase in endothelial nuclei of the tubules. This is followed later by leukocytic infiltration and displacement of the lumen. The powerful rush of blood to the glomeruli produced by a simultaneous rise in blood-pressure and cardiac enlargement causes distention of the glomeruli. The restoration of the patency of the latter is part of the healing process, the blood in the urine being part of the phenomenon, its amount serving as a gauge of the progress of the healing. Sometimes thrombosis of the capillaries causes new obstruction, with death from cardiac paralysis as a possible result. And in rare instances diffuse infiltration may lead to loss of function of the glomeruli, the formation of adhesions and to epithelial proliferation with chronic nephritis as a possibility.

Escherick and Schick distinguish between *septic scarlatinal nephritis* and *glomerular nephritis*. The septic type forms a part of the general septic process and can be expected to occur where the streptococcic infection causes severe necrotic pharyngeal changes. The degree of anatomical modification greatly exceeds that of the clinical manifestations. The urine contains more or less albumin and nephritic sediment, but blood is not visible macroscopically, nor is the amount much diminished. While the streptococcus is properly regarded as the etiological factor in this form of nephritis, the histology of glomerular nephritis does not justify such a supposition, even though streptococci have been recovered from the urine in the latter. Escherick and Schick consider the glomerular nephritis to be a so-called toxic or excretory nephritis. It is entirely possible, they believe, that streptococci present in the blood in late stages of scarlet fever may pass through the diseased kidneys into the urine without contributing to the pathological process in the kidneys. This bacteriuria raises the interesting question whether or not other microörganisms, as well as streptococci, and particularly the unknown inciter of scarlet fever, can leave the body by way of the urinary canals, and suggests the possibility that, as in typhoid fever, the urine of scarlet fever may play a part in the spread of the disease. While scattered reports in literature indicate such a possible infectivity of the urine, there as yet is no accurate demonstration of the fact.

ENDOCRINE GLANDS.—The endocrine glands are not generally considered as contributing to the pathology of scarlet fever, but French writers, more especially Hutinel and others, have recently insisted upon the importance of adrenal and pancreatic insufficiency in the syndrome of scarlet fever, and in interesting histological studies have demonstrated cellular and glandular changes on which they base their claim. Hutinel has also observed isolated instances of slight modification of the thyroid gland and also one case in which changes in the hypophysis were present. Although these changes were always associated with modifications in the suprarenal gland, it is conceivable, he thinks, that they may occur independently.

OSSEOUS AND NERVOUS SYSTEMS.—The *bone marrow* in septic cases sometimes is found to contain small collections of round-cells and minute streptococcic foci, the latter being partly intravascular and partly free in the tissue. Jochmann claims, in such instances, to have found streptococci present in the *spinal cord.*

BLOOD.—The chief interest in the blood changes in scarlet fever centers around the leukocytosis and inclusion bodies. Leukocytosis is already noticeable during the incubation period and reaches its maximum at the height of the disease. In mild cases it ranges from 17,000 to 34,000; 14,000 to 40,000 in severe cases. Differential count shows also a change in the eosinophils. They are either decreased or disappear at the onset of the fever, rising later and remaining high until convalescence sets in.

The chief value of the blood-count is a diagnostic one. Increased in leukocytes in a suspected case of scarlet fever with an ill-defined or aberrant rash will serve to distinguish it from measles in which leukocytosis is not present; or when a person has been exposed to the disease, leukocytosis during a possible incubation period will strengthen the suspicion of the existence of scarlet fever. In doubtful cases well-marked eosinophilia on the third or fourth day will also be of diagnostic value.

SKIN.—With few exceptions investigators interpret the skin changes in scarlet fever as the result of an inflammatory process. According to the researches of Pearce, the changes are not pronounced until after the third day of the disease; i.e., from the fifth to the tenth day he was able to note marked infiltration of the epithelium and the connective tissue with polymorphonuclear leukocytes. The lymphatics were much dilated and also contained polynuclear leukocytes. The leukocytic infiltration had disappeared from specimens taken on the twelfth day of the disease.

Rach, in a more recent study of the histology of the skin in scarlet fever, describes the process as an acute inflammation with an exudate which is at times serous and at others multicellular and hemorrhagic, the predominating cells being polymorphonuclear and neutrophile leukocytes. The inflammation is manifested in the skin by more or less dense foci (individual punctæ or efflorescences). The favorite site of the punctæ appears to be around the orifices of the hair follicles, but they often protrude beyond that area, either owing to edema of the underlying cutis or to accumulations of the exudate in the epidermis. This follicular swelling thus represents the anatomical basis for the typical scarlatinal minute papulous punctæ.

The changes were observed in various stages with gradual transition from one to another. The first stage is that of exudation in which (*a*) the exudate leaves the vessels and enters the upper layer of the cutis, and (*b*) enters the epidermis where it accumulates and gives rise to the microscopic vesicles, which often are also visible to the naked eye. The second stage is desquamation with the shedding of incompletely hardened (parakeratosis) particles of epidermis.

The fact that the efflorescences in various stages were seen side by side indicates that the exanthem develops at successive stages.

Historical Summary.—The works of Galen, Rhazes and other ancient writers contain various descriptions of a disease with throat symptoms and a diffuse red eruption suggesting scarlatina, but not until the sixteenth century was the disorder differentiated from measles by Ingrassias of Naples. The first accounts of what appears unmistakably to be scarlatina are those of Daniel Sennert, of Wittenberg, and his son-in-law, Michael Doerring (about 1625). They give us the typical picture of scarlatina, the rash, desquamation, joint pains, anasarca and delirium. Sydenham (in 1676), however, was the first to present a careful analysis of the disease with its medical characteristics and to give it the designation scarlatina or scarlet fever. He also differentiated it from measles, with which it was constantly being confused. The epidemic which gave Sydenham the opportunity for studying scarlet fever in large numbers was evidently a mild one, since he believed the disorder scarcely deserved to be considered a disease. But he was destined to change this belief fifteen years later when an epidemic of unusual malignancy, described by Mortons, broke out in England. Huxham (1740) appears to have been the first to call attention to the importance of angina in the symptom-complex of scarlatina.

The disease was common in Europe during the eighteenth century and from the middle of that era spread over both hemispheres. According to Caiger, it first appeared in the North American Colonies in 1735, spreading over New England, reaching New York in 1746, thence extending to the coast states. By 1791 it made its appearance in the interior, reaching Canada and the Northern states during the early part of the nineteenth century. South America was not invaded until about 1830, and since then the disease has appeared often and at times in severe epidemic form, in nearly all of the countries of that part of the continent. During the middle of the nineteenth century scarlatina was reported from Polynesia, New Zealand, Tasmania, Australia and in distant Greenland and Iceland (in 1827 in the latter).

The disease appears irregularly in epidemics of greater or less virulence, often extending over a period of years; in large centers of civilization, however, it is always more or less prevalent.

BIBLIOGRAPHY

ANTHONY, B. V. H. Some characteristics of the streptococci found in scarlet fever. New York City Health Dept., Research Lab. Collected Studies, 1907, iii, 62.

BERNHARDT, G. Die Aetiologie des Scharlachs. Hypothesen die nicht Bakterien, sondern Protozoön zum Gegenstand haben. Ergebn. d. inn. Med. u. Kinderh., 1913, x, 358.

Bowie, J. M. The leukocytosis of scarlet fever and its complications. Jour. Path. and Bacteriol., 1902, viii, 82.

Caiger, F. F. Scarlet fever: in Allbutt and Rolleston's System of medicine, Vol. II, part 1, p. 410. London, 1906.

Cantacuzène, J. Inoculation de la scarlatine aux singes inférieures. Compt. rend. Soc. de Biol., 1911, lxx, 403, 405.

Caronia, G. Sulla presenza di speciale anticorpu nel siero di sangue di bambine scarlattinosi. Pathologica, 1914, vi, 97.

Cooke, W. E. Hyperthyroidism following scarlet fever. Jour. Roy. Army Med. Corps, 1916, xvii (2), 114.

Di Cristina, G. Osservazioni e richerche sulle reazione immunitarie spontanee o provocate nella febbre scarlattinosa. Pediatria, 1916, xxiv, 385.

Di Cristina, G., and Pastore, R. Richerche di immuno-profilassi nella febbre scarlattinosa. *Ibid.*, 1919, xxvii, 1.

Dublin, L. I. A study of 1153 cases of scarlet fever with special reference to sequelæ. New York, 1916.

Dutoit, A. Ueber die Erkrangung der Nebennieren beim Scharlach. Klin.-therap. Wchnschr., 1915, xxii, 209-211.

Escherich, T., and Schick, B. Scharlach. Wien, 1912.

Florand, A. L., and Meklen, P. Rhumatisme et troubles cardiaques dans la scarlatine. Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, xl, 985.

Garrison, F. H. History of medicine. Philadelphia, 1917.

Goodall, E. W., and Washburn, J. W. A manual of infectious disease. London, 1908.

Graham, J. R. Scarlet fever: symptoms and diagnosis. New York Med. Jour., 1915, cii, 556.

Griffith, J. P. Crozier. Scarlet fever: in Forchheimer's Therapeusis of internal medicine, Vol. II, p. 114. New York, 1913.

Harmsen, E. Akute Blutungen in folge von Scharlach, und andere tödliche Blutungen aus dem Ohr. Beitr. z. Klinik d. Infektionskr., 1914, iii, 159.

Hektoen, L. Bacteriologic examination of the blood during life in scarlet fever with special reference to streptococci. Jour. Am. Med. Assn., 1903, xl, 685.

Hutinel, V. Les pneumo-scarlatine. Arch. d. méd. d'enf., 1916, ix, 71.

——— Les pleuresies scarlatines. Bull. méd. de Par., 1916, xxx, 89, 101.

——— Les lesions des capsules surrenales dans la scarlatine. Arch. f. Kinderh., 1913, lx, 21, p. 397.

Jochmann, G. Lehrbuch der Infektionskrankheiten. Berlin, 1914.

Ker, C. B. Infectious diseases. London, 1909.

Klimenko, W. N. Blutungen bei Scharlach. Beitr. z. Klin. d. Infektionskr., 1914, iii, 439.

Kling, C., and Widfelt, G. Serotherapy of scarlet fever. Hygiea, Stockholm, 1918, lxx, 2; Abstr. Brit. Med. Jour., 1918, ii, 93.

Koch, R. Ueber Scharlachreconvalescentenserum. Münch. med. Wchnschr., 1913, lx, 2611.

Kolmer, J. A. Leukocytic "inclusion bodies," with special reference to scarlet fever. Am. Jour. Dis. Child., 1912, iv, 1.

——— Study of streptococcic antibodies in scarlet fever with special reference to complement reactions. Arch. Int. Med., 1912, ix, 220.

Relation of streptococcus to scarlet fever with active immunization by means of streptococcic bacteria. Penn. Med. Jour., 1911-1912, xv, 360.

Landsteiner, K., Levaditi, C., and Prašek, E. Tentatives de transmission de la scarlatine au chimpanzée. Compt. rend. Soc. de biol., 1911, lxx, 641.

Landsteiner, K., Levaditi, C., and Danulesco, V. Contribution à l'étude de la scarlatine experimentale. *Ibid.*, 1912, lxxii, 358.

Mallory, F. B. Scarlet fever: protozoön-like bodies in four cases. Jour. Med. Research, 1904, v, 483.

Mallory, F. B., and Medlar, E. M. The etiology of scarlet fever. Jour. Med. Research, 1916, xxxiv, 127; *ibid.*, 1916-1917, xxv, 209.

McClure, J. C. Handbook of fevers. London, 1914.

McCollom, J. Scarlet fever: in Osler's Modern medicine, Vol. II. p. 334. Philadelphia, 1907.

McVail, J. C. The prevention of infectious diseases. London, 1907.

Minor, T. C. Scarlatina statistics of the United States. Cincinnati, 1875.

Nobécourt, Jurie des Camiers, and Tournier. Rhumatisme articulaire, endocardite et pericardite dans la scarlatine. Bull. et mém. Soc. méd. d. hôp. de Paris, 1918, xxxix, 793.

Pearce, R. M. Scarlet fever: its bacteriology and gross and minute anatomy. Med. and Surg. Rep., Boston City Hospital, 1899.

Place, E. H. Scarlet fever: in G. C. Shattuck's Principles of treatment.

Pospischill, D., and Weiss, F. Ueber Scharlach (der Scharlacherkrankung, zweite Teil). Berlin, 1911.

Pryer, R. W., and Sewell, G. The etiology of scarlet fever. Jour. Lab. and Clin. Med., 1918, iii, 524.

Rach, E. Beitrag zur Histologie des Scharlachausschlages. Beitr. z. path. Anat. u. allgem. Path., 1909-1910, xlvii, 455.

Ramond, F., and Chambas, G. Deux complications de la scarlatine: le rhumatisme et l'ictère scarlatineuse. Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, xxxix, 770.

Reis, E., and Jungman, P. Die Behandlung schwere Scharlachfälle mit Reconvalescentenserum. Arch. f. klin. Med., 1912, cvi, 70.

Schleissner, F. Die Aetiologie des Scharlachs. Ergeb. d. inn. Med. u. Kinderh., 1913, x, 342.

Sharpe, C. T. Cerebral edema in scarlet fever. Jour. Nerv. and Ment. Dis., 1917, xlvi, 283.

Simon, J. Manifestations cardiaques chez le soldat au cours de la scarlatine. Thèse de Paris, 1913.

Simonin, M. J. Pleurésies suppurées au décours de la scarlatine chez l'adulte. Bull. et mém. Soc. méd. d. hôp. de Paris, 1909, xxvii, 643.

Smillie, W. W. The Beta-hemolytic streptococci. Jour. Infect. Dis., 1917, xx, 45.

Stegeman, A. Die pathologisch-anatomischen Veränderungen des Myokards und der Herzganglien beim Scharlach. Jahrb. f. Kinderh., 1914, lxx, 491.

Teissier, P., and Duvoir, M. Pleurésies au cours de la scarlatine chez l'adulte. Bull. et mém. Soc. méd. d. hôp. de Paris, 1909, xxvii, 547.

Tileston, W., and Locke, E. A. The blood in scarlet fever. Jour. Inf. Dis., 1905, ii, 375.

Tracey, S. E. A simple and efficient means of applying artificial heat. Jour. Am. Med. Assn., 1910, lv, 1443.

Weaver, G. H. The treatment of scarlet fever with immune human serum. Jour. Infect. Dis., 1918, xxii, 211.

Welch, W. W., and Schamberg, J. F. Acute contagious diseases. Philadelphia, 1905.

Woody, S. S. Exanthemata; scarlet fever: in DaCosta's Handbook of medical treatment. Philadelphia, 1918.

Zingher, A. The use of convalescent and normal blood in the treatment of scarlet fever. Jour. Am. Med. Assn., 1915, lxv, 875.

——— A simple syringe method for the transference of blood from donor to recipient; its aplication in the treatment of scarlet fever and other conditions. Arch. Pediat., 1914, xxxi, 912.

CHAPTER XIII

RUBEOLA

(*Measles*)

BY WILLIAM A. JENKINS, A.M., M.D.

Definition, p. 281—Etiology, p. 281—Symptomatology, p. 283—Incubation, p. 283—Invasion, p. 284—Eruption, p. 286—Desquamation, p. 288—Laboratory findings, p. 288—Diagnosis, p. 288—Association with other diseases, p. 289—Complications, p. 289—Sequelæ, p. 290—Treatment, p. 291—Prophylaxis, p. 291—Curative treatment, p. 292—Prognosis, p. 298—Pathology, p. 299—History, p. 300.

Definition.—Rubeola is an acute infectious, readily transmissible disease of unknown origin, characterized clinically by a well-marked catarrhal process of the mucosa of the upper air passages and a characteristic exanthem.

Etiology.—PREDISPOSING CAUSES.—Any constitutional defect, any disease process or pathologic change which tends to lower the individual resistance constitutes a predisposing factor; likewise any environmental factor which would fall below what would be considered the standard would be classed in the same category. Exposures to cold, the race, sex, soil, altitude, climatic considerations and seasonal changes exert very little influence in this disease.

As to age, the disease is almost unknown under six or eight months (there is very little chance for outside exposure during the nursing period). An infant may be born with measles, the eruption showing on the body at the time of birth, the condition being transmitted through the placental circulation, the mother having had it during the later weeks of pregnancy.

From two to twelve or fifteen years of age is the commonest period for the appearance of measles. From twenty to forty years the disease is fairly common only. Measles is uncommon in old age. (This may be partly explained by the fact that in many instances the individual has had the disease in childhood.)

Previous Attacks.—It is quite possible that an individual may have a second or possibly even a third attack of measles. The observers whose opinions are most worthy of consideration are agreed on this statement. It is not, however, at all common. As a rule, one attack of true measles confers immunity for life, and it is certain that very many of the reported cases of second and third attacks were simply mistaken diagnoses. Either the individual had a simple attack of urticaria, erythema, an attack of rubella (German measles) or, as occasionally happens, some fugitive skin irritation or a drug eruption was carelessly spoken of as an attack of mild measles.

Panum, Rosenstein, Willand and other men who have paid very close attention to the exanthemata and have had a very rich experience state that they have never seen a second infection of true measles.

EXCITING CAUSES.—As was stated in the definition, measles is a disease of unknown origin, the special organism never having been isolated. Extensive examinations of the blood, tissues, secretions and excretions have been made. Microscopical examinations and cultural experiments have been carried out by experts under the most rigid and technical scientific requirements. The results were negative in every instance. The causative organisms are found in the blood. We have conclusive proof of this in the authentic, recorded cases of experimental inoculation, furnished in the literature of the subject.

Inoculation was first attempted at the direct suggestions of Munro, at Edinburgh, in 1758. The method was briefly as follows: Small superficial cuts were made across the measles spots in a selected portion of the body, the subject having a typical case of measles. Clean, soft cloths were placed in contact with the above-mentioned cuts and were allowed to become soaked with the exuding material. Then, a series of small cuts or openings in the skin were made on the arms of healthy individuals who had never had measles, and these soaked cloths were now loosely bound over the cuts for two or three days. Measles usually developed promptly, according to these observers. Cloths thus soaked retained their infectious possibilities for about ten days. Work of this character was carried out in Italy, England and the United States of America, some observers making as many as a thousand inoculations. The above experiments demonstrate that the disease is a transmissible one, that experimental inoculation is possible, and that the specific organism is present in the blood of the infected individual.

Experimental inoculations were successfully made also with the discharges from the mucous membranes of the upper air-passages; in fact, speaking from the standpoint of the experimental production of the disease, this proved to be the surest and easiest way, and it accords with our present-day conception of the chief method of transmission of this disease from one individual to another, namely, the secretions from the upper air-passages. These early investigators, in their inoculative experiments, gathered the fresh secretions from the upper air-passages of a known case of measles and placed them in contact with the upper air-passages of healthy individuals; the disease developed promptly in from eight to ten days. Contrary to statements of some observers, the consensus of opinion seems to be that the epidermal scales and tears do not contain the causative organism, as the inoculative experiments recorded along these lines were always negative or doubtful.

Modes of Conveyance.—In the great majority of instances this disease is transmitted by a direct or contact infection. There is no doubt that its chief method of transmission is by means of the secretions of the upper air-passages. Therefore, every object or article which has in any way come in contact with a case of measles has been exposed to contamination from these secretions and may therefore carry the disease. For example, clothing, playthings, handkerchiefs, towels, fomites of any sort may be responsible for transmitting the disease. It is to be remembered, however, that the organism is not supposed to live on contaminated articles mentioned above longer than ten days. Individuals coming into the room and coming into direct contact with the sick individual may carry the specific organism of the disease on their persons and their clothing.

To illustrate, we have records of a healthy person, e. g., a physician visiting and examining a case of measles in an infected locality and then traveling for a considerable distance into an isolated community and spending the night with a family. After fourteen days measles broke out in this household. Later investigation proved the above means or route to have been the only possible explanation of the appearance of the disease.

Symptomatology.—For the sake of convenience and discussion, it is customary to divide the subject into periods: namely, (1) Incubation; (2) Invasion; (3) Eruption; (4) Desquamation.

(1) INCUBATION.—The incubative or hatching period embraces the interval between the implantation of the causative agent on the selective tissue of the host and the manifestation of symptoms. This definition will hold good for the incubative period in all infectious diseases, whatever the location or character of the infection may be. Much needless confusion has arisen in medical literature from an improper conception, on the part of medical authors, of the true limits of this period. Likewise, this same confusion exists with reference to what is going on in the body of the infected individual during this period.

Many authors in their descriptions of the whole group of the exanthematous diseases conceive the incubative period as lasting from the time the organism gains entrance into the system until the first appearance of the eruption (exanthem). Such a conception is manifestly incorrect, as it would include the invasional or prodromal symptoms as part and parcel of the incubative period. Again, in cases of known exposure (the exact time and the attending circumstances having been carefully noted, afterwards proven by the prompt appearance of the disease) it is all too common for some over-zealous observers to seize upon any small happening, e.g., malaise, headache, slight fever (all fugitive in character), or, in fact, any physiological perturbation whatsoever, and dignify the condition by speaking of it as a symptom of the incubative interval, when as a matter of fact the symptom in question was merely a coincidence and might just as well have happened to the individual had he never been exposed to an infection.

When disease-producing microörganisms (animal or vegetable)—infectious agents, in other words—gain entrance into the human host, they must first find a part or tissue of the body where conditions are suitable to their growth and multiplication, and when they have found such a location, the incubation may be said to have begun, and not until then. Now, after the organism is appropriately located, a certain amount of time is necessary before the organism can prepare or elaborate a sufficient amount of poison to react on the fluids and tissues of the body and thus produce definite symptoms (which is the name that we give to such reactions). Scientifically speaking, the above comprises the true incubative interval. This period is a variable one and depends on the one hand on the amount, character or kind and virulence of the invading organisms, and, on the other, on the particular type of tissue invaded. Direct inoculations, experimental or accidental, always appear to shorten the incubative interval, because in direct inoculation, the microörganism is placed at once in contact with its selective tissue and under the most favorable conditions, consequently growth immediately begins (we skip the pre-incubative stage).

Now, when an infection is contracted in the ordinary clinical manner, the organism has gained entrance into the body, but it may be detained in any unfavorable location for quite an appreciable period of time (the pre-incubative interval), before it is finally transported to its particular selective tissue, where growth readily begins. From the foregoing considerations, then, we can readily see that the incubative interval is, clinically speaking, a quiescent period and from the very nature of the case there can be no symptoms in this period.

Perhaps in the future, when the intricacies of the science of immunology are better understood and the discovery of new and improved methods of investigation have enabled us to scrutinize more deeply the phenomena of infections, certain serological or cytological phenomena may be developed which may be said to constitute symptoms of the incubative interval. At the present time we have no such advanced methods or facts. The incubative period of measles is, therefore, void of symptoms. From the standpoint of time, the incubative interval of this disease may be said to be from ten to fourteen days. Fourteen days seem to be the period of choice with most authors.

(2) INVASION.—When the exciting cause (microörganism) of measles, after implantation on its selective tissue, has elaborated sufficient poison to react on the tissue-cells and fluids of the body, thus causing physiological perturbation (symptoms), we are confronted by the phenomena or symptoms of invasion. The period of invasion (sometimes spoken of as the prodromal stage) begins rather suddenly or abruptly and lasts, as a rule, three or four days (exceptionally five or six days or even longer). The symptoms manifesting themselves during this period may be classified or grouped under three heads, viz.: (*a*) general or systemic disturbances, (*b*) catarrhal symptoms and (*c*) the symptoms of the enanthem.

(*a*) *General or Systemic Disturbances.*—We often notice that there is a coated tongue with loss of appetite. The child complains of being "sick at the stomach," with even nausea and vomiting in some cases. The patient exhibits a "desire to lie around" and does not feel like doing anything—general malaise as we physicians call it. Headache, chiefly frontal in character, is commonly exhibited. Some fever is almost universally present and in typical cases the behavior or curve of the fever is definitely characteristic. It begins with the other symptoms of onset and rises to a peak in twenty-four to forty-eight hours (usually about the second day). It then remits to rise again to a second acme or high point before or just at the full flush of the exanthem. Careful observations compiled from our records of epidemics in child institutions, orphan asylums and the like enable us to verify the above, for under such circumstances we have competent nurses who may be taught to observe and record all symptoms from the most fugitive beginning prodromal symptoms up to the time the child is discharged.

This class of work has convinced clinicians that the fever curve of measles is prone to exhibit two peaks or high points, one occurring in the prodromal state (about its mid-point), the other during the height of the eruption. It is likewise a commonly accepted dictum that if we take a view of the entire febrile curve of the disease, we will note a tendency on the part of the fever to exhibit a slight morning remission and evening exacerbation.

Now and then we may have some enlargement of the lymphatic glands about the neck and under the jaw. This, however, is neither a characteristic nor a diagnostic feature. In certain severe and malignant epidemics, cases are occasionally seen which manifest very grave and alarming symptoms, even in this early period, the patient passing rapidly into a somnolent or typhoid-like state or even becoming comatose with great prostration supervening. It is to be understood, however, that the above, while it may possibly occur, is not in any sense to be considered as forming part and parcel of the typical syndrome of measles.

(*b*) *Catarrhal Symptoms.*—The catarrhal symptoms present themselves early. They are characteristic and are sufficiently well marked and constant to be of real diagnostic value. In the first few hours, there is a sense of fullness or a stuffy feeling about the nose; sneezing may be frequent. The throat feels dry and sore. Next the nasal secretions begin, the nose runs, the acrid secretions irritating or even excoriating the upper lip. The pharyngeal ring becomes reddened. Now we have a typical nasopharyngeal catarrh. At the same time a brassy cough (with or without hoarseness) appears. A mild type of bronchitis may be present at this stage.

The ocular conjunctiva begins to show evidence of irritation and inflammation. First the eyes hurt and feel as if there were particles of dust under the lids. The conjunctiva becomes reddened, photophobia develops. Secretion is increased; the lids tend to stick together in the morning and in extreme cases the eyes are swollen and blood-shot. The catarrhal symptoms persist throughout the prodromal period. They usually increase or become accentuated as the eruption or exanthem develops and likewise subside as the eruption subsides.

(*c*) *The Enanthem* (*the Internal Eruption*).—Usually about the end of the second day of the invasional period, on the mucosa of the mouth and throat, there appears an eruption. The mucous membrane takes on a dark-red color and is much engorged. Dark-red elevated spots appear from a pinpoint to a pea in size, most common and most typical about the pharyngeal ring, noticeable also on the roof and floor of the mouth, and to a lesser extent, on the mucous membrane of the lips and cheeks.

Very frequently we notice, on the mucosa of the roof and floor of the mouth and lips, another type of spots. They are most commonly found on the mucous membrane of the cheeks, about opposite the molar teeth. These spots are slightly elevated, of a dark-red color and are about the size of a pinhead, and the center of each spot is occupied by a minute, white or bluish-white speck. These are called Koplik's spots, so named after the physician who first called definite attention to them.* Koplik's spots are hard to distinguish unless one has a very strong light. Strong daylight is best. These spots are believed to be present in from 90 to 95 per cent. of cases. Many authors regard the spots as being of great diagnostic value. Still others of wide clinical experience do not regard the Koplik's spots as possessing any especial value from the standpoint of diagnosis, claiming even to have found them in other of the exanthematous diseases.

The finding of typical *Koplik's spots* a day or two before the eruption, especially in the presence of marked catarrhal symptoms, strengthens the possibility of a pre-eruptive diagnosis. This is particularly true if we are dealing with epidemics, if we have knowledge of the diseases that are prevalent in given areas, or if we know that there has been a definite exposure. In all isolated, sporadic cases, we are confronted by a very different proposition. By way of conclusion, then, we may say that the finding of Koplik's spots adds another sign to the symptom group. It is another bit of evidence, another link in the chain, and is of value to just that extent. The finding of the spots could never make the diagnosis positive. On the other hand, the absence of the spots could never exclude the diagnosis.

Their time of greatest value is early in the disease, as they appear most promptly with the enanthem and tend to change character and fade as the eruption comes out.

We should, perhaps, make mention of the fact that the enanthem occasionally spreads by continuity of structures into the larynx, sometimes producing an alarming edema and even invading the mucous membrane of the bronchial tubes. Other observers have reported cases of involvement of the mucous membrane of the stomach and duodenum. The literature of the subject likewise furnishes reports of a few instances of involvement of the mucosa of the rectum and the vulva. Care should always be exercised to avoid mistaking thrush, and aphthous stomatitis for the Koplik's spots, as either of these conditions may occur as an early complication. A consideration of their individual distribution and character should, however, prevent error.

(3) ERUPTION.—In typical cases, the eruption is prone to appear on the fourth day (it can appear earlier or one, two or several days

---

* See article by Koplik, *Archives of Pediatrics*, Dec., 1896.

later). The rash appears first as small red spots (macular, quickly becoming elevated or papular) on the forehead and sides of the face about the cheek bones, often showing behind the ears. Then the neck, chest and trunk are involved, likewise the arms and hands, legs and feet are invaded by the eruption. The palms of the hands and the soles of the feet may be red and injected, the eruption rarely becoming papular in these locations; the same may be said of the hairy scalp.

Usually the rash spreads rapidly, often covering the entire body in 24 hours; again it may take two or three days. The small red papules quickly increase in size and sometimes coalesce. The individual spots may vary in size from a pinhead to a common bean. The color commonly deepens and may be purplish or violaceous. The spots occur in irregular patches, splotches or clumps over the surface of the body. The old writers speak of the patches as having a crescent shape.

The eruption may be scattered thinly over the body or it may thickly stud the entire body. The eruption persists for some days, about four or five days or a week on the average. Then it quickly fades. The fading process follows the order of the appearance of the spots, head first, then neck and chest, body, legs and arms. The deep purple of the spots fades and they tend to have a brownish shade; slight pigmentation remains for two or three weeks.

Variations of the Rash.—Reliable authors have reported cases (observed in epidemics) without a rash. The rash is occasionally very slight, lasting only a day or so. It may appear on only a small part of the body. On the other hand, it may be unusually prolonged, lasting two weeks. In very severe and fatal forms of the disease, the rash may be hemorrhagic (black measles). The rash may appear to be under the skin, not coming to the surface well. Heat and warmth tend to bring out the eruption, while exposure to the cold or even chilling may serve to retard its appearance.

The character of the eruption is modified somewhat by various pathologic states of the skin, namely, eczema, psoriasis, erythema, etc. Relapses of the eruption are recognized as possibilities. They have been observed and recorded occasionally by reliable observers.

The progress of the other symptoms during the eruption are as follows:

Fever.—The fever reaches a second peak or high point a few hours before or at the time of the full bloom of the eruption. Then it subsides, usually rather gradually, for two or three days, occasionally rather quickly, like a crisis. A big rise in temperature after the rash has been out several days most likely means a complication. A few hours before the eruption, even, the face looks puffed and is slightly red and has a rather mottled appearance. The red color of the eruption deepens and takes on a purplish shade and becomes markedly papular or elevated to the touch. The legs and forearms show the spots last.

Catarrhal Symptoms.—The catarrhal symptoms of the invasional stage are still present and increase. The coryza increases. There is an irritating discharge from the nose. Photophobia is intense. The eyes are likely to be blood-shot. The lids tend to stick together. The voice may be hoarse, with a brassy, troublesome cough, with mucous râles present over the chest. A thick tenacious mucus is expectorated. It is the rule for the catarrhal symptoms to subside as the eruption disappears. Their persistence would suggest a complication. The tongue is moist and coated usually with a white fur. The appetite is poor, there is present some nausea or vomiting and occasionally diarrhea.

(4) DESQUAMATION.—The subsidence or disappearance of the eruption marks the beginning of the desquamation period (the *convalescent state*, as it is often called). In a given case, if there are no complications, the patient improves rapidly, appetite returns, thirst disappears, photophobia is gone, the catarrhal symptoms gradually leave, although slight cough, bronchitis and soreness of the throat may persist. A slight branny scaling of the skin takes place and in ten days or two weeks the patient is well. There is, however, a marked susceptibility to external influences in this period. They should be examined and supervised throughout the period.

LABORATORY FINDINGS.—The laboratories are well-nigh useless to us in this disease. Some authors claim a slight leukocytosis in the incubative period and the first part of the invasion, stating that before or as the eruption comes out, the leukocytosis disappears, and we may have a leukopenia. They also state that the polymorphonuclear leukocytes are liable to be increased during the attack, dropping back to the normal as defervescence takes place. The blood findings are neither characteristic nor dependable. Albuminuria is a common finding and the same may be said concerning an occasional cast.

Diagnosis.—The diagnosis is based chiefly on the catarrhal symptoms and the exanthem. A characteristic exanthem is always the strongest point in the diagnosis of this disease. Second in value is the character and behavior of the catarrhal symptoms, plus the enanthem, with the accompanying spots of Koplik. The average case of measles, after the appearance of the eruption, is not likely to be mistaken for anything else. Before the eruption appears, it is always hazardous and difficult, and many times impossible, to make a diagnosis. Many shrewd clinicians always keep themselves posted as to what infectious diseases are prevalent in certain areas or localities, likewise they keep themselves posted regarding the matter of possible exposures on the part of their patients—and they use this knowledge in drawing conclusions.

In isolated, sporadic cases, where no infection, contact or exposure can be traced, where the case seems to come out of a clear sky, diagnostic difficulties arise. A case fulfilling the conditions mentioned above can never be diagnosed positively in the pre-eruptive state. Many cases of influenza, in the early stages, present a picture very like that of the prodromal state of measles. In the literature of the subject, we find instances where physicians have experienced difficulty in differentiating this disease from typhoid and typhus fever, etc., in the early stages. The other exanthematous diseases also are a common source of diffi-

culty in the early stage. Drug eruptions and erythemata are sometimes confusing.

The diagnosis should never be made on one feature alone. The case should be considered in its entirety. In doubtful cases, it is always best to wait for the appearance of the eruption before coming to a definite decision.

Association with Other Diseases.—The association of other diseases with measles (a double infection), which occasionally happens, always tends to increase our diagnostic difficulties as well as increase the danger to the patient. Among those diseases mentioned as having occurred rather commonly in connection with measles, we have the following: variola, varicella, vaccinia, scarlatina, rubella, typhoid fever, diphtheria, whooping cough, etc. The double infection is an accidental one. There is positively no relationship existing between the two diseases. No specific chemical or biological affinity can be said to exist. The laws or rules governing the successful implantation of one infection apply equally to the other, and in no way whatsoever does the one depend upon the other for its presence. The relationship is purely accidental or incidental.

Complications.—When any typical symptom of measles gets to be sufficiently severe, or accentuated, as to occupy a position of importance in the progress of the case, that symptom may be spoken of as constituting a complication. Likewise when any morbid process or intercurrent disease implants itself on the individual, when that individual is already the subject of an attack of measles, the resultant process may be said to constitute a complication.

THE SKIN.—Miliary vesicles may appear among the papules. Simple erythemata or urticarial processes may occur at any time throughout the disease. Secondary infections of the papules with microörganisms, commonly staphylococci, may rarely cause a few pustules to appear. Chronic skin eruptions, if present, will influence or modify the character of the eruption. Among the skin diseases which occasionally complicate measles may be mentioned eczema, psoriasis, erythema, impetigo, pemphigus, etc.

THE EYE.—An intense conjunctivitis may appear; edema of the lids is occasionally present. Keratitis and iritis are likely to occur in scrofulous children. Corneal ulcerations, phlyctenular ulcerations and granular lids are among the rare complications. The inflammatory process may extend and plug the lacrimal gland. Hordeolum or sty and blepharitis marginalis may be present.

THE NOSE.—Inflammations and secondary infections of the nasal mucosa occasionally appear. The pharyngeal ring is commonly inflamed. The eustachian tube may become plugged and inflamed, fail to drain properly and produce by extension an inflammation of the middle ear.

THE EAR.—Simple catarrhal processes of the eustachian tube are quite common. If the patient has enlarged tonsils and adenoids, the likelihood is much increased. The eustachian tube does not drain well, the inflammation extends up into the middle ear and the drum may rupture. We have a typical case of otitis media. Measles, according to the statistics, causes from 2 to 10 per cent. of the diseases of the ear and fully 10 per cent. of all running ears are due to measles. Ear involvements, therefore, are very common, and through this channel the meninges and even the brain substance may be involved.

THE AIR-PASSAGES.—Simple laryngitis, edema of the larynx and tracheobronchitis are encountered frequently. Pneumonia, especially in poor, impoverished, debilitated children, is one of the commonest, as well as the ugliest, complications with which we have to deal. The type is most commonly lobular, although the lobar type may occur. Pleurisy, empyema and even tuberculosis occasionally present themselves.

THE GASTRO-INTESTINAL TRACT.—The frequency of the different types of stomatitis has already been mentioned. Diarrhea is occasionally seen in epidemics and in severe cases, and even serous peritonitis has been described as occurring. It takes place by direct contiguity of structures from the inflamed and infiltrated walls of the intestinal tract.

THE KIDNEYS.—Albuminuria, a few casts and slight granular or cloudy swelling of the special structures of the kidney are quite frequently present, and occasionally true acute parenchymatous nephritis occurs.

THE HEART.—This organ is not commonly involved during the active stages of measles. If this organ is involved at all, the disease is most likely to occur as a sequel. An occasional tachycardia or other rhythmic disturbance may be present.

THE NERVOUS SYSTEM.—The nervous system is not ordinarily affected. Such disturbances as do occur are more of the nature of temporary or functional aberrations than otherwise. There are a few cases, however, in which meningitis, neuritis and brain substance involvement are encountered.

Frequently diphtheria and whooping-cough may be epidemic in the same locality with the disease under discussion, hence, either of these diseases may complicate measles.

Sequelæ.—A sequela (from *sequor*, meaning *to follow*) is a condition which arises or persists in the patient after the original infection has departed. The following items always exert an influence on the character, type and likelihood of appearance of sequelæ. First, external factors, e.g., dampness, unhygienic quarters, undue exposure during the early part of the disease in question, lack of treatment, improper treatment, etc. Second, internal (or personal) factors, e.g., all unfavorable influences existing in the constitution of the individual: (*a*) structural and functional defects or deficiencies; (*b*) disease taints (constitutional dyscrasias), e.g., scrofula, rickets, tuberculosis, chronic Bright's disease, etc.; (*c*) the character and virulence of the infectious organisms.

THE AIR-PASSAGES.—Any disease or condition which may appear as a complication may likewise appear as a sequel. This is true of all infectious diseases. In considering the sequelæ of measles, the air-passages easily take first rank. Laryngitis, bronchitis and pneumonia, lobular or lobar, are quite common. A persistent harassing bronchitis is very prone to hang on and give us trouble. Lobular pneumonia is exceedingly frequent, especially in young, weak children, as stated above. Tubercular engraftment is always a possibility. Empyema occasionally appears.

THE EAR.—This organ is likely to furnish us with sequelæ. It has been stated that from 5 to 10 per cent. of our cases of permanent total deafness and middle ear disease (otitis media) with running ears, are directly traceable to an old attack of measles. All too frequently do we hear our patients say, "I have never heard well out of that ear since I had measles," or "That ear has been running off and on ever since I had measles."

THE KIDNEYS.—Almost every experienced clinician can from his case history files, produce a few records of acute Bright's disease which are definitely traceable back to a case of measles.

Practically all long and severe cases of measles will show a fair grade of anemia on making a blood-count. In fact, it is quite within the range of possibility for almost any organ or tissue of the body to exhibit some impairment as a direct result of measles. For example, a young healthy boy 12 years of age developed measles. The family doctor was called when the eruption appeared. He prescribed, and left directions for the conduct of the case (the boy was not confined to bed). Just two weeks from the date of the doctor's visit to the case, he was called in again. He found the boy in bed, face and hands swollen, feet and legs swollen as high up as the knees. Pitting on pressure, anemic mucous membranes, pain across the back, urine scant, red and cloudy. Examination of urine showed: Albumin abundant and hyalin and granular casts present. Diagnosis: acute parenchymatous nephritis, following measles. Inquiry disclosed the fact that this boy had been playing out in the grass in the lot adjacent to the house, in his bare feet after the dew had fallen. (The case occurred in the early summer.)

Treatment.—PROPHYLAXIS.—Our experience in epidemics teaches us that this disease is readily transmissible. We have every reason to believe that the causative agent is a filterable one. We feel quite sure that the disease is transmitted chiefly by the secretions from the nose, mouth and throat of the diseased individual. The organism is certainly in the blood, and may possibly be in the discharges from the gastro-intestinal tract. These latter routes, however, do not furnish a very favorable opportunity for transmission from one individual to another. It is a fairly sure conclusion that it is chiefly the secretions of the nose, mouth and throat, as mentioned above, that we have to watch particularly.

The mode of transmission is most commonly direct from person to person. We know, however, that it is transmitted indirectly through articles, clothing or fomites, recently soiled with the secretions and discharges mentioned above. It is more than likely that the organisms do not live longer than about ten days on soiled articles or fomites.

The disease is communicable from the very earliest catarrhal symptoms (or even before that), until all traces of secretions have disappeared from the nose and throat.

With the above as a summation of our actual knowledge regarding the causative agent, its method of transmission and its period of communicability, we may formulate methods of control which will apply to the individual himself and likewise the community of which he is a member.

The methods commonly used to prevent the spread of acute infectious diseases are, in general, about the same everywhere. We can do no better than accept the rules laid down for the control of communicable diseases in the report of the American Public Health Association Committee on Standard Regulations, appointed in October, 1916. They are as follows:

> "METHODS OF CONTROL.
>
> "(A) *The infected individual and his environment:*
>
> "1. Recognition of the disease: Clinical symptoms. Special attention to rise of temperature. Koplik's spots and catarrhal symptoms in exposed individuals.
>
> "2. Isolation: During period of communicability.
>
> "3. Immunization: None.
>
> "4. Quarantine: Exclusion of exposed susceptible school children and teachers from school until 14 days from last exposure. This applies to exposure in the household. Exclusion of exposed susceptible children from all public gatherings for the same period.
>
> "5. Concurrent disinfection: All articles soiled with the secretions of the nose and throat.
>
> "6. Terminal disinfection: Thorough cleaning.
>
> "(B) *General measures:*
>
> "1. Daily examination of exposed children or other possibly exposed persons. This examination should include record of the body temperature. A non-immune exposed individual exhibiting a rise of temperature of 0.5° C. or more should be promptly isolated pending diagnosis.
>
> "2. Schools should not be closed or classes discontinued where daily observation of the children by a physician or nurse is provided for.
>
> "3. Education as to special danger of exposing young children to those exhibiting acute catarrhal symptoms of any kind."

CURATIVE TREATMENT.—Many cases of measles, even in epidemics, are so mild that little or no treatment is required. On the other hand, a given case or an epidemic may be so severe that it will tax the therapeutic ingenuity of even the most experienced clinician and give us a very high mortality as an end-result. We can, therefore, give no rigid, definite, inflexible plan that will apply to all cases. Every case is a law unto itself.

We may as well acknowledge at the start that we have no specifics. **Sera, vaccines** and **immunizing agents** are (up to the present time, at least) useless in this disease. Attempts have been made (with blood serum taken from convalescent patients) to inoculate individuals against measles; the serum has also been used with curative intent during the disease. No clinical results worth considering have resulted in either case. We likewise have no **drug specifics.** The treatment is purely symptomatic. We shall take the subject up as follows: (1) *General management*, which shall include such measures as would apply to the average case; second, *the treatment of special symptoms* (such as are prone to occur in severe cases).

(1) *General Management.*—The patient should be isolated in a suitable, comfortable room and a fairly even temperature maintained—from 65° to 70° F. (18.3° to 21.1° C.). Such arrangements should be made as will secure an adequate supply of **fresh air** for health and breathing purposes. (It is well to remember that fresh air need not necessarily be cold air.) The bed-clothing should be sufficient for warmth and comfort at all times. The old notion that the patient should be placed in a **darkened room,** for fear of injury to the eyes, is, of course, a mistake. If there is a high grade conjunctivitis present, with marked photophobia, make use of **colored glasses,** an eye shade or screen. These measures, however, are rarely necessary. It is best to have some fixed rule, applicable to all of the infectious exanthematous diseases, as regards **antiseptic precautions** as applied to the patient and all articles which are used by or come in contact with him. Also the method of caring for the discharges and emanations of the patient should come under the same rule. (*See* Prophylaxis.)

The *nurse* should exercise average care to prevent the possibility of carrying the disease to others. After examining a case of measles, the attending *physician* should always wash his hands and apply some alcohol, and before going to see another patient, he should always be out in the open for a while. In epidemic work in an institution, he should always wear a gown.

The erroneous notion that **water** is harmful in cases of measles is common among the laity. Water may be used freely, internally and externally. Every patient should receive a daily cleansing **bath** of warm soap suds and water, throughout the disease.

The **diet** in the average case of measles should be light, nutritious and easily digested. If the case is severe and gastro-intestinal symptoms are present, we must modify the diet to meet the requirements of the case. Plenty of fluids should be insisted on in all cases. Fruit juices and acidulated drinks are commonly acceptable to most patients, especially to children.

In the beginning of the attack, the bowels should be well cleaned out. **Calomel** is one of the best agents for this purpose. It may be used alone or combined with other suitable drugs. It may be given in a single dose or in broken doses, according to preference. The calomel should always be followed in a few hours by a dose of **oil** or a **saline.** Later an **enema** will usually suffice to keep the bowels open.

The upper air-passages should be kept open and clean by the frequent use of warmed simple antiseptics in the shape of **gargles** or **sprays.** Solutions containing **boric acid** (one dram (4.0 grams) to the pint), **carbolic acid** (5 drops to the ounce), and **bicarbonate of soda** (one dram (4.0 grams) to the pint), are good agents for the purpose.

The eyes should be washed out frequently with a warm **boric acid solution** or a **normal saline solution.** The presence of a cough will sometimes require a few doses of one of the standard (N. F. or U. S. P.) **anodyne expectorants.**

Many physicians are in the habit of administering a few moderate doses of **quinin** in the invasional or early eruptive stages, partly for its influence on the fever and partly, as they claim, to bring out the eruption. For the latter effect, many use **hot drinks,** e.g., hot lemonade, afterwards covering up the patient with **blankets.**

The writer recalls a justly celebrated pediatrist and medical teacher (long since dead) who always gave, as a routine measure throughout the disease, what he called his "**fever mixture.**" It is as follows:

Sp. ætheris nitrosi	f ʒ ii (8 c.c.)
Potassii acetatis	ʒ ii (8 grams)
Aq. camphoræ Liq. ammonii acetatis	āā f ℥ iss (45 c.c.)

M. Ft. Sol. Sig.: Teaspoonful in water every four hours (for a child under 5 years of age; above 5 years, increase the dose).

He claimed that this prescription was of great value, in that it lowered the temperature and increased the elimination of waste by the kidney route and protected these organs at the same time.

To relieve the itching during the eruptive and desquamative stages, the body should be anointed daily (after the cleansing bath) with **carbolized vaselin,** 5 drops to the ounce. The period of convalescence should always be closely scrutinized for possible complications and sequelæ.

(2) *Treatment of Special Symptoms.—The Eyes.*—The eyes should always be kept clean. They should be washed out once or twice a day in the average case. A medicine dropper or a piece of absorbent cotton may be used, and plain, warm **water, normal saline solution** or **boric acid solution** (2 to 5 per cent. or even a saturated solution) applied. The saturated solution or boracic acid may be used every few hours if necessary. If pus is present, a solution of **argyrol** 10 per cent. to 15 per cent. should be dropped into the eyes, one or two drops every three or four hours, or according to indications. The margin of the **lids** may

be **anointed with vaselin** before the child goes to sleep, to prevent sticking in severe cases.

Nose, Nasopharynx and Mouth.—**Cleanliness** and mild **antiseptics** are always indicated here: first, to inhibit the spread of the disease, as the secretions from these parts furnish the chief mode of the conveyance of the disease; second, and equally important, to prevent complications. Congestion furnishes mechanical difficulties, e.g., plugging of the eustachian tube, and it also favors the implantation of other organisms on the part (mixed infection). We readily see, then, how important it is to keep these parts clean. In mild cases, simple substances used as **gargles** and **sprays** (by means of an atomizer) are effective, e.g., **Dobell's solution, boric acid, sodium bicarbonate,** and various other mild antiseptic solutions.

Chlorazene (chloramin), the new Dakin antiseptic, is being tried out rather extensively just now in epidemics in the army camps. It is used in a fresh 1-1,000 or 1-500 solution. It is to be freely sprayed into the nose, pharynx and throat every few hours. Pus on the tonsil or in the pharynx should be touched with **nitrate of silver** or other suitable agent.

The following prescription makes an excellent gargle:

Spts. vini rectificati Aq. menthæ piperitæ	āā........f ℥ ii	(60.0 c.c.)
Formalin	f ʒ i	(4.0 c.c.)
Aq. destil. q. s. ad..............	f ℥ viii	(240.0 c.c.)

M. Ft. Sol. Sig.: Use as a gargle every 2 or 3 hrs.
(full strength or diluted one-half in plain water).

The Bowels.—The bowels should be opened at the start with **calomel** and a **saline** as noted above. The indications after that would depend on the condition of the gastro-intestinal tract. If the tongue be clean and belly flat, an enema every other day would suffice. If the reverse of these conditions obtain, there can be no objection to the use of simple purgation throughout the disease as needed. Occasionally diarrhea appears. When this feature is present, the **diet** should be modified accordingly and the indicated remedies applied.

Fever.—A moderate degree of fever (103° or 104° F. [39.4° or 40° C.]) in this disease holds no especial significance. The temperature tends to reach a high point for only a very short time in most cases (from the last day or so of the prodromal stage until the eruption attains its maximum). **Hydrotherapy** is the best measure, by all odds, to combat the fever. Sponging with warm or tepid water is best. The full **bath** is left for extreme cases. Occasionally, just at the highest point of the fever, when the eruption is just blooming out and the child is restless, hot, coughing frequently and delirium seems near, it is legitimate to use the following prescription every two to four hours for two or three doses:

℞

Codeinæ sulphatis	grain ⅛	(0.008 gram)
Caffeinæ citratis	grain ss	(0.032 gram)
Acetphenetidini	grains iii	(0.2 gram)

M. Ft. Capsulæ No. 1. Sig.: One capsule every 2 to 4 hours. This prescription is suitable for a child 5 years of age or older.

One or two doses is usually sufficient to quiet the patient, reduce the fever one or two degrees and allow him to fall asleep. **Coal tar derivatives** are never used as a routine measure. Prolonged temperature, after the eruption is all out, is usually due either to a complication or to severity of the disease. **Hydrotherapy, stimulants** and the proper attention to the complication present, would meet the demands of the case here.

The Ear.—Congestion and infiltration of the eustachian tube, and even earache, are quite common as special symptoms, and otitis media occurs very frequently. The best treatment is prevention. **Spraying the nose and throat,** relieving congestion and keeping the parts clean with **chlorazene** or other suitable antiseptics is best. If, in spite of these measures, there is some earache, dry heat may be tried, applied locally, or 5 per cent. carbolic acid in glycerin may be used. A few drops of this warmed and dropped into the ear every three or four hours is often efficacious.

If the earache increases in severity, inspect the drum membrane frequently by means of the head mirror and ear speculum. If the symptoms increase, with marked restlessness and rise of temperature, and if the drum membrane is tense, red and bulging, **incise** it in the lower posterior quadrant with a small thin-bladed bistoury (or paracentesis knife). After incision the pus, which flows out freely, should be wiped out every few hours with a soft pledget of cotton on an applicator. After the ear is cleaned, very gently wash out the ear with a small rubber syringe, using for the purpose a saturated solution of **boracic acid** in water. If the discharge should suddenly cease, the symptoms increase and the temperature jump up, with swelling and tenderness appearing behind the ear, the mastoid cells have likely become involved and a mastoid operation may be necessary.

The Skin.—Mention was made above of measures to bring out the eruption, e.g., **quinin** internally, **sinapism to the chest, hot drinks** and **blankets,** etc. While many of us use such measures infrequently or not at all, still we have no legitimate reasons for bitterly condemning them, so long as they do not injure the patient in any way, as it is commonly conceded by most clinicians that the case does best in which the eruption follows the type in both time and appearance. On the other hand, when the eruption is "driven in," as the laity say (inward measles), i.e., if it fails to come out, the cases are severe and complications are more likely to occur. For example, a young child is frequently brought to the outpatient clinic of a hospital in bad weather, in the late prodromal stage of measles. (We make a tentative diagnosis at the time and the subsequent history of the case verifies it.) The eruption is tardy and imperfect and the clinical course of the disease is stormy. The intense itching is to be relieved by **bicarbonate of soda solutions,** one dram to the pint, or **carbolized vaselin,** 5 drops to the ounce. **Olive oil and oil of eucalyptus,** equal parts of each, applied daily, is good to relieve the itching and it likewise protects the skin during desquamation.

Air-Passages.—(*a*) *Laryngitis.*—This is a very common symptom in the early part of measles. It is very easily recognized by the croupy, stridulous character of the breathing and voice sounds. **Local applications** are very efficacious, **compresses,** either **hot or cold. Ice-water cloths** applied for a few minutes at a time is about the best method. **Inhalations** by means of a croup kettle and tent, **of compound tincture of benzoin and oil of eucalyptus** (of each a teaspoonful to the quart of water) are effective. Sprays may be used in the same way. When edema of the larynx is present, incorporate in the **spray** enough **adrenalin chlorid** to make a 1-20,000 solution and use it frequently. **Scarifying** or **local blood-letting** and even **intubation** are measures that are resorted to in extreme cases. If marked laryngitis should occur late in the disease, suspect diphtheria, and make a diligent search for it.

(*b*) *Bronchitis.*—Mild bronchitis with a dry, troublesome cough is often present as a prodromal symptom even. It may persist all the way through or appear at any stage of the attack, or even remain as a sequela after the attack is gone. The measures mentioned under laryngitis may be useful in the beginning of bronchitis. **Mustard paste,** or **cold compresses** alternating with heat, are useful at times. The cough which prevents rest and sleep must be controlled. The **sulphate** or **phosphate of codein** (grains $^1/_{16}$, $^1/_8$, or $^1/_4$, according to age) (grams 0.004, 0.008 or 0.016) is the most efficacious remedy.

If the child is old enough to expectorate, we use some of the simple **anodyne** and **sedative combinations** of the United States Pharmacopeia or National Formulary. A suitable dose of **codein** may be added to each dose of the above, if necessary. In the severer types in small children, say under three years, use strychnin sulphate (grains $^1/_{240}$), apomorphin hydrochlorid (grains $^1/_{120}$ every three or four hours, with nourishing food and support. If the patient is an adult or even an older child, use some of the stimulating expectorants, e.g., **syrup of hydriodic acid,** tablespoonful every four hours.

Minute amounts of **codein** may be added to any of the above, if the character of the cough demands it. A cough which drags along into convalescence and even increases in severity suggests tuberculosis or bronchopneumonia. Pneumonia, most commonly bronchopneumonia (occasionally the lobar type), may occur as a complication of measles. (For the treatment of either type, see articles on these diseases.)

The Kidneys.—Albumin is almost universally present in measles. In the adult, casts are frequently found also. True nephritis is a possibility at any time. The urine should be kept bland and abundant, which can be accomplished by protecting the skin and administering plenty of **fluids**, especially water. The "fever mixture" prescription mentioned above is likewise useful. If nephritis arises, the appropriate treatment should be administered.

The Heart.—It is very uncommon for this organ to be involved by the disease under consideration. The average doctor practicing in a small place might go a lifetime and never see a case. The man of large experience will encounter a case occasionally. The order of frequency of involvement of the cardiac structures is as follows: first, endocarditis; second, pericarditis; third, myocarditis. (For treatment, *see* chapters on the Heart.)

The Nervous System.—The nervous manifestations most frequently encountered in measles are physiologic or functional in character. They are prone to occur at the acme of the disease or in severe cases. They are usually toxic manifestations, viz., irritation of nerve centers, produced by the presence of the toxins of the disease. The patient may be restless, highly nervous and tossing about, unable to sleep; occasionally he lapses into a muttering, incoherent, semidelirious state. **Hydrotherapy** properly applied usually relieves the above. Sometimes we make use of the **bromids** or the following prescription:

℞

Codeinæ sulphatis	grain ⅛	(0.008 gram)
Caffeinæ citratis	grain ss	(0.032 gram)
Acetphenetidini	grain iii	(0.2 gram)

M. Ft. Capsulæ No. 1. Sig.: One every 2 to 4 hours for 2 or 3 doses. (This prescription is suitable for a child 5 yrs. of age or older.)

If coma is present, we have passed the above stage. The indications now are to support, stimulate and eliminate. Still more rarely we may have meningitis, neuritis, etc.

Prognosis.—In the average case the prognosis is good. However, in view of the special knowledge which physicians have of this disease, experience would teach us to make a reserved or guarded prognosis. By the laity, measles is regarded as a simple disease. Ordinarily they will say, expose the child and let him have the disease and be done with it. Our experience and the trend of the literature of the subject teach us to be more careful.

The mortality varies in different epidemics and the percentages given in the textbooks varies anywhere from 3 to 50 per cent. The prognosis has always been found to be grave when the disease is introduced for the first time into an isolated community.

To give us some true conception of the possibilities which this disease has as regards severity and mortality, it will be profitable for us to glance in a cursory way at the history and behavior of some of the great epidemics that have occurred in various parts of the world, especially in savage and uncivilized lands. (*See* writings of Hirsch.) An epidemic occurred along the course of the Amazon River in 1749 and about 30,000 of the natives died. An epidemic occurred in the Hudson Bay district in 1846. Fully 50 per cent. of the native Indians had the disease severely and the mortality was high. In the Fiji Islands an epidemic occurred (described by Squire and Cruikshank) and 20,000 of the natives died, or about one-fourth of the population, roughly speaking. The disease was so severe that the natives fled in terror, deserting their own sick. Dysentery and congestion of the lungs of the severest forms existed as complications. According to the literature in some of the temporary hospitals in the vicinity of Paris (at the time of the Franco-Prussian war in 1871) the mortality from measles reached as high as 40 per cent. Exposure to the elements, unhygienic and unsanitary surroundings, the absence of proper care, food and medical attention, all played a part, of course, in determining the severity of the epidemics just referred to.

The above citations, selected almost at random from the exceedingly rich literature of the subject, serve in a very forceful way the purpose of impressing upon our minds the possibilities of measles under certain circumstances. Furthermore, physicians of the present generation who have had opportunities for wide experience in epidemic diseases will vouch for the statement that all the terrors and possibilities of measles are not confined to the literature of the past. The whole question, then, of the prognosis of measles is not so simple a proposition as it first appears to be on superficial examination; much depends upon the type and character of the individual epidemic. And perhaps still more depends upon the attendant circumstances which surround and accompany the epidemic.

The prognosis is likewise usually bad when this disease breaks out in army camps, barracks, prisons, etc. The presence of severe complications also raises the mortality percentage and adds to the gravity of the prognosis.

Pathology.—There is very little true pathology in this disease and that pertains chiefly to the skin and mucous membranes, and even this disappears when death occurs. The pathology, therefore, in most cases is that of the complications and sequelæ. There are, however, definite changes in the skin and mucous membranes. First, in the *skin:* There is present an hyperemic process of the superficial vessels of the skin with dilatation and extravasation of blood elements. A round-celled infiltration takes place, the sweat and sebaceous glands are dilated and their coils are packed with round cells. Small hemorrhages may occur and colloid degeneration of cells takes place, which is supposed to account for the appearance of the papillæ. There is likewise a catarrhal process of the *mucous membranes,* namely, hyperemia and extravasation of blood elements, denuded epithelium, the presence of blood-cells and possibly minute ulcerations. The so-called black or septic types of measles are most likely due to an hemolytic streptococcus. They are characterized by rapid blood disintegration, marked subcutaneous hemorrhages with such parenchymatous changes as are found in grave septic processes, e.g., in the liver, spleen, kidneys and possibly even the heart.

History.—This disease comes to us out of the remote past; its origin reaches back perhaps into unknown antiquity. It occurred in epidemic form throughout Asia and Europe and was carried to America by the early settlers. Thence, by the streams of exploration, immigration and commerce, it spread to South America, Africa, Australia and even to the Islands of the Sea. The etymology of the term "measles" is not well nor definitely worked out. The following are some of the sources to which it is traced: From "Maselen" (Dutch); from "Masern" (German); from "masura" (Sanskrit), masura meaning spots; and from "maselen" (Fourteenth Century English), etc.

What appears to be a fairly intelligible description of both measles and small-pox was first found in the writings of one Ahrun, a native of Alexandria, a physician by occupation (and a priest also, it seems), A. D. 610 to 641. The first approximately adequate description of measles is accredited to Rhazes, A. D. 900, and about equal credit is given to Avicenna, A. D. 980 to 1037. Rhazes called the disease "hhasbah" and indicated its separation from smallpox. Withering definitely distinguished measles from small-pox in 1792. Thomas Sydenham (an Englishman) by his brilliant articles drew a distinct line between scarlet fever and measles in 1655.

The term "rubeola" (meaning red) is from the Arabic and was supposed to have been applied first by Haly Abbas in the latter part of the tenth century. This appellation was in turn replaced by the term "morbilli" (Italian), meaning little disease (as compared to small-pox with which it was at that time so frequently confused). The term "morbilli" remained in use until well along in the Eighteenth Century, when Sauvages suggested a return to the use of the term "rubeola," which suggestion was adopted by Cullen and Willan. The term "rubeola" is now the recognized and accredited name for this disease among all English-speaking races.

CHAPTER XIV

RUBELLA

(*German Measles—Roetheln*)

By William A. Jenkins, A.M., M.D.

Definition, p. 301—Etiology, p. 301—Symptomatology, p. 301—Incubation, p. 301—Invasional or prodromal stage, p. 302—Eruption, p. 303—Desquamation, p. 305—Diagnosis, p. 305—Differential diagnosis, p. 306—Complications and sequelæ, p. 306—Treatment, p. 307—Prophylaxis, p. 307—Curative treatment, p. 308—Prognosis, p. 308—Pathology, p. 309—History, p. 309.

Definition.—Rubella may be defined as an acute, specific infectious disease of unknown origin, characterized by a rather long incubative period, short or absent prodromes, mild faucial catarrh, enlargement of the cervical glands and a polymorphous eruption.

Etiology.—Just as in the case of rubeola, so in this disease we may say that climate, season, altitude, soil, sex, race and heredity seem to exert little if any influence. Exposure to cold lowers resistance and thus acts as a predisposing factor. The same may be said of overcrowding, filth, lack of light and poor hygienic surroundings generally. Rubella is essentially a disease of childhood; it is uncommon during the nursing period; fully 75 per cent. of the cases occur under 15 years of age. The disease is rare after puberty, and almost unknown after forty. (One or two cases reported in the literature at 70 years.) Clinically speaking, one attack of this disease is supposed to confer immunity. As a rule, we look upon the report of second attacks as mistakes in diagnosis. (Second attacks are possible, but their occurrence must certainly be very rare.) The organism producing this disease has never been isolated. The chief mode of conveyance is by direct contact. Individuals coming in contact with the disease may act as carriers, even when they do not contract the disease themselves. Towels, clothes, handkerchiefs, bedclothing, etc., coming in contact with and having been soiled by the patient are capable of carrying the disease. The chief clinical method of conveyance of this disease is undoubtedly the secretions from the mouth, nose and throat.

Symptomatology.—We shall consider the symptoms under the following heads: (1) Incubation; (2) Invasion; (3) Eruption; (4) Desquamation.

(1) Incubation.—When we attempt to fix a definite and scientific time-limit for the incubative interval of this disease, our difficulties are many and serious. In the first place, it is highly probable that the pre-

incubative interval may be rather long in this disease, i. e., the specific organisms may gain entrance into the system but may remain localized, say in the mucosa of the bronchial tubes, before they invade the general system via the systemic circulation. They have not as yet reached their especial selective tissue. The true incubation has not begun. Secondly, the prodromal period of this disease is notoriously untrustworthy. It eludes all of our attempts to classify it definitely. Occasionally, though infrequently, it may last three or four days. More commonly it lasts only a few hours. In many instances it is apparently absent altogether. This difficulty is a real one and helps to make our calculations untrustworthy. Again it may be that the life-cycle of the causative organism is unusually long as compared to the life-cycle of some of the other infectious agents belonging to this group. To illustrate, the life-cycle of the scarlet fever organism (reasoning from clinical grounds) must be quite short, while in the case of the disease under discussion the life-cycle may be long. We frequently have opportunity (especially in epidemics) to note that a healthy child was definitely and positively exposed to this disease at a certain time, and we may note the appearance of the first symptoms. This is about as close as we can get to the problem. Even this procedure does not take into account the possible error due to the variability of prodromes. A series of successful artificial inoculations, carried out according to rigid scientific requirements, would help us to some extent in our difficulty, but we have no such data. By common agreement the time-limit of the incubative interval of rubella is placed at from two to three weeks.

(2) Invasional or Prodromal Stage.—There is no such thing as a definite characteristic group of symptoms pertaining to this period. As a general rule the symptoms are mild in character and of short duration—12 to 48 hours—rarely 48 hours or longer; e.g., the child does not feel well, a slight headache is complained of, and if the temperature is taken at this point we usually find a slight rise present (99° or 100° F. [37.2° or 37.8° C.]). There is a fairly constant and definite enlargement of the lymphatic glands about the neck, the posterior auricular, anterior cervical, the submaxillary or all of these groups may be involved. Occasionally a sore throat presents itself, or it may be a mild conjunctivitis; again hoarseness with a brassy cough (mild bronchitis) may present as a prodromal symptom.

A strong, healthy, robust child may not complain at all. The symptoms are overlooked. Hence, some authors speak of cases without prodromal symptoms, the rash being in such cases the first symptom to present itself. The writer, in his experience with epidemics of rubella occurring among children in an institution, has taken occasion to watch and tabulate, with the assistance of a trained nurse, the symptoms of the prodromal period. The method pursued was as follows: After the appearance of a case of this disease, all of the exposed children (eating at the same table and playing and sleeping in the same dormitory) were inspected, interrogated, their throats examined and temperatures taken daily up to the time of the appearance of the eruption; with this method symptoms were unearthed that under ordinary circumstances would have passed unnoticed. The commonest symptoms noted in mild cases were headache, slight malaise, enlarged glands, and some temperature. It was astonishing how frequently we found (12 to 24 hours before eruption) a temperature of 99° or $99°_{+}$ F. (37.2° or $37.2°_{+}$ C.), practically never over 100° F. (37.8° C.). The prodromal period may be prolonged, e.g., cough and hoarseness with bronchitis and a temperature of from 100° to 103° F. (37.8° to 39.4° C.) may be present for two or three days before the eruption comes out. Very rarely we encounter an instance in which general or systemic symptoms are pronounced and severe in the prodromal stage. There is always some redness and congestion about the mucosa of the upper air passages, with a tendency to the appearance of some irregular slightly elevated reddish spots (the enanthem). This latter, however, is in no wise characteristic. Finally, it is to be remembered that any symptom of rubeola (measles) in the prodromal stage may be duplicated by rubella in the same stage. Fortunately, however, in rubella the given symptom is much milder and there is no definite and characteristic group of symptoms.

(3) Eruption.—The eruption of this disease usually appears promptly after 24 hours (or rarely 48 hours) of mild prodromal symptoms. Many authors speak of it as the first symptom to appear. More properly speaking it is often the first symptom to attract attention. Whenever we have a definite eruption it is practically certain that some mild prodromal symptoms were present, although they may have been overlooked or disregarded. The mild erythematous reddening or suffusion of the face which is so common in measles a few hours before the appearance of the eruption, never appears in rubella. The eruption comes out promptly, showing first about the face, then the trunk, next the arms and legs, the order of the appearance of the eruption being practically the same as it is in measles. The eruption passes from the macular to the maculo-papular (sometimes entirely papular) stage, the individual spots are from a pinhead to a split pea in size, usually smaller than the spots of measles. As a rule, the spots are more discrete; there is not much tendency to confluence. The color is usually not so bright a red—more of a faded rose. The eruption covers the body quickly, usually in 24 hours, rarely over 48 hours. Likewise the spots fade rapidly, beginning about the face first, thence on down the body, following the order of the appearance of the rash. Oftentimes the spots are fading on the face when they are at their height on the legs. The duration period of the rash is in the average case three days. (Often a shorter period, rarely a longer one.)

The above is a fairly accurate picture of the average rubella eruption. Let us now turn our attention to some of the *anomalies* or *irregularities* of the rash of this disease. The eruption is sometimes fugitive in character or even absent; only a few spots may show on the chest or back, quickly fading. Cases reported in which there was no definite eruption discoverable are certainly well authenticated. It is not uncommon in epidemics where a number of children are taken sick at about the same time, most of them showing the usual eruption. To note a case with malaise, enlarged glands, slight fever and some catarrhal symptoms without eruption, under the circumstances mentioned above, there can be no reasonable doubt as to the diagnosis; however, another possible way of accounting for this rare condition presents itself—as the eruption is fugitive in character, lasting only a few hours, the physician did not get an opportunity to see it. If the case should occur in the physician's own family, where opportunity would be afforded to examine the naked body of the child daily throughout the illness, it is more than likely that some spots would have been detected at some time. The eruption may bloom out all at once, occurring on all parts of the body simultaneously. Occasionally the eruption may show only on one area or part of the body, e. g., the chest. The rash in this disease shows no special tendency to become congregated into clumps or blotches. Relapses or recurrences in which a second or even a third crop of eruption comes up are occasionally encountered, the interval being usually from a few days to two weeks.

We noted in the definition of rubella that the disease was characterized by a polymorphous eruption. Accordingly some authors mention the morbilliform type (the type which resembles measles). This is the common type, and it must be admitted that rubella does seem to bear some close relationship to measles. Many of the older writers were of the opinion that rubella was a sort of hybrid form of measles.

Next we read of the scarlatiniform type, where the eruption very closely resembles scarlet fever, rendering diagnosis difficult in some instances. We note in the literature of the subject reference made to observers who thought that rubella might be a mixture of measles and scarlet fever (so-called mixed type), with mention of particular cases in which the eruption resembled measles on one part of the body and scarlet fever on another. Regarding this phase of the subject, we may safely make the following generalizations: First, that in the greater percentage of all cases, the eruption resembles very closely that of measles; second, that the cases in which the eruption resembles that of scarlet fever (to the degree that diagnosis becomes difficult) are to be considered as relatively rare, although we must admit that we do see fairly frequently cases in which the spots are wholly macular, of a faded or wild rose color (not the fiery red of scarlet fever), varying in size from a pinhead to that of an adult's finger-nail.

The progress of other symptoms during the eruptive stage are as follows:

Fever.—It is quite characteristic in the eruptive stage to have some temperature, although often slight (rarely over 100° F. [37.8° C.], but occasionally reaching 102° or 103° F. [38.9° or 39.4° C.]), and of short duration. This fever has no characteristic curve and no peaks or high points. The temperature usually shows in the prodromal stage and tends to rise slightly until the eruption reaches its acme, then quickly declines coincidently with the eruption. The above is the usual course. If we have complications, or if the individual resistance is poor, or the infection severe and the disease prolonged, the fever behaves accordingly.

Catarrhal Symptoms.—Catarrhal symptoms, if present in the invasional period, persist throughout the eruptive period or even longer; or they may first present themselves with the eruption and remain after it has faded. A coryza of the nasal passages, redness and soreness of the throat, laryngitis, slight hoarseness and mild bronchitis constitute the symptoms commonly seen under this heading. The eye ordinarily escapes. It may be slightly reddened; some epidemics are reported in which a rather severe conjunctivitis was a prominent symptom. Therefore, concerning the catarrhal symptoms, we may say that it is possible to have in this disease any catarrhal symptom that is found in measles; likewise its grade of severity may be the same. Rarely do we have a group of symptoms. It may be the eye, the nose, the pharynx or the bronchial tubes, any one of these singly. Frequently catarrhal symptoms are slight or absent, and they are never sufficiently dependable to be of diagnostic value in this disease.

Glandular Enlargement.—Enlargement of the posterior auricular, anterior cervical or submaxillary glands, any one or all of these groups may participate in the process. Some enlargement is present in from 50 to 75 per cent. of all cases of rubella. (Some observers say 90 per cent.) This symptom shows during the invasional stage and lasts throughout convalescence, sometimes even longer. These glands generally undergo resolution, rarely do they suppurate. When suppuration does take place it is the result of mixed infection. In a few instances, in severe cases, the glands of the axilla and groin have participated in the enlargement. Enlargement of the cervical glands is sufficiently characteristic of this disease to be considered a symptom of diagnostic importance.

(4) DESQUAMATION.—As the eruption fades, usually the accompanying symptoms likewise disappear, and these events bring us to the threshold of the period of desquamation. It is unusually short and uneventful. In the average case the skin shows a type of discoloration, often having the appearance of a brownish stain (the remains of the eruption). This stage lasts two or three days in very mild cases and a week or ten days in severer cases. The phenomena of this period will, of course, vary with the severity of the disease and particularly with the amount and type of the eruption. A marked eruption will show considerable discoloration of the skin and most commonly a fairly perceptible branny or scaly desquamation. With a milder character of eruption, the desquamation is less marked or imperceptible. The enlargement of the cervical glands remains throughout this period and sometimes considerably longer.

Diagnosis.—The diagnosis in the average or type-case of rubella is to be made in the main by consideration of the following points: (1) the absence or mild character and short duration of the prodromal stage; (2) the characteristic enlargement of the cervical lymphatics;

(3) the eruption—its rapid appearance, its polymorphous character and its rapid subsidence; (4) the extremely mild character and short duration of the whole process, and its comparative freedom from complications and sequelæ. The laboratory does not furnish us with any data of importance in making the diagnosis in this disease. Diagnosis in sporadic cases is sometimes entirely impossible. For the differential diagnosis between rubeola, rubella and scarlet fever, *see* the accompanying table.

Differential Diagnosis of Rubeola, Rubella and Scarlet Fever

	Rubeola	Rubella	Scarlet Fever
Period of Incubation.	10 to 14 days.	14 to 21 days.	2 to 5 days.
Prodromal Symptoms.	Coryza of upper air-passages (marked). Cough, conjunctivitis, moderate fever.	Often absent (?) mild catarrh, sore throat, cervical glands enlarged almost constantly.	Short duration, headache, high temperature, sore throat, rapid pulse.
Time of Appearance of Eruption.	4th day (rarely later) on the face and neck.	2nd day. Face or upper part of trunk.	24 to 48 hours; neck and chest.
Appearance and Development of Eruption.	Macule then papule size, split pea to that of a bean. Color—red, changing to a dusky or violet shade; spots show in groups or clusters. The eruption shows over entire body (usually). Duration 4 to 5 days.	Eruption polymorphous. Common type; resemble measles; spots are not so red nor so large, evenly distributed—no groups nor clusters. 2nd type macular, faded rose color; size, pinhead to finger-nail. Eruption disappears in 2 to 4 days.	Punctate, intensely red or fiery red. Slightly rough to the touch. Confluent, appears continuous (a reading glass will show tiny points of white skin all through the eruption). Region of mouth and nose free of eruption.
Eruption of Mucous Membranes.	Well-marked and characteristic, especially "Koplick's spots." Small pinhead-sized, reddish spots capped by minute bluish-white points, shown best on cheek opposite molar teeth. Present 24 to 48 hours before skin rash.	Slight maculo-papular-enanthem, about same time as skin-rash (or slightly before, neither characteristic nor diagnostic).	Sore throat, tonsils enlarged. "Strawberry tongue."
Constitutional Symptoms.	Proportionate to severity of eruption.	In average cases, very little if any.	Usually severe; all symptoms increase with the eruption.
Fever.	Fever-curve has two peaks or high points, one about the middle of the invasional period; the other at the full bloom of the rash.	Very slight as a rule, beginning a few hours before the rash; reaches its highest point as rash comes out.	Usually high; appears even before the rash, rises with the rash and constitutional symptoms and usually disappears with them.
Desquamation.	Branny scales, the rule being 5 to 7 days.	Usually hardly perceptible; may show as fine scales. 3 to 5 days.	Begins in 6 to 10 days. A characteristic symptom. Occurs as flakes or strips, sometimes even casts. There may be 2 or 3 crops of it.
Complications and Sequelæ.	Air-passages, ear, eye, kidneys.	In the average case, none.	Nephritis; ear, throat.
Inoculability.	Secretions from the nose, mouth and throat. The blood.	Secretions from the nose, mouth and throat. The blood.	Secretions from the nose, mouth and throat. The blood.

Complications and Sequelæ.—In this disease complications and sequelæ occur infrequently. It is the rule for cases to recover promptly without further difficulty. Speaking, then, from a broad clinical standpoint, we have only a very small percentage of complications and sequelæ. A debilitated condition, a severe epidemic, exposure or lack of attention during the attack, all favor the development of complications and sequelæ. The following are some of the conditions occasionally encountered: (*a*) in the mouth and throat: stomatitis, tonsillitis, pharyngitis, catarrh of the eustachian tubes with ear-ache and possibly otitis media; (*b*) in the air-passages: laryngitis, bronchitis and pneumonia; (*c*) in the nervous system in malignant cases we occasionally have high fever, rapid prostration and convulsions or delirium; (*d*) in the urinary system: attacks of true nephritis are occasionally encountered as sequelæ of this disease.

Treatment.—PROPHYLAXIS.—Our experience in epidemics teaches us that this disease is readily transmissible. We have every reason to believe that the causative agent is a filterable virus. We are quite sure that the disease is transmitted chiefly by the secretions of the nose, mouth and throat of a diseased individual. The microörganism is certainly in the blood. It is a fairly sure conclusion, however, that it is chiefly the secretions of the nose, mouth and throat that we have to watch in particular. The mode of transmission is most commonly direct from person to person. We know, however, that it is transmitted indirectly through articles, clothing or fomites recently soiled with the secretions and discharges mentioned above. It is probable that the organisms do not live longer than about 10 days on the soiled articles or fomites. Some authors claim that the organisms may live as long as from 20 to 30 days on soiled articles, as, for example, bedding.

The disease is communicable from the very earliest catarrhal symptoms (or even before that), until all traces of secretions have disappeared from the nose and throat.

With the above as a summation of our actual knowledge regarding the causative agent, its method of transmission and its period of communicability, we may formulate methods of control which will apply to the individual himself and likewise to the community of which he is a member.

The methods commonly used to prevent the spread of acute infectious disease are, in general, about the same everywhere. We can do no better than accept the rules laid down for the control of communicable diseases in the report of the American Public Health Association Committee on Standard Regulations Appointed in October, 1916. They are as follows:

"METHODS OF CONTROL

"(A) *The infected individual and his environment:*

"1. Recognition of the disease: Clinical symptoms.

"2. Isolation: Separation of the patient from non-immune children and exclusion of the patient from school and public places for the period of presumed infectivity.

"3. Immunization: None.

"4. Quarantine: None except exclusion of non-immune children from school and public gatherings, from the eleventh to the twenty-second day from date of exposure to a recognized case.

"5. Concurrent disinfection: Discharges from the nose and throat of the patient and articles soiled by discharges.

"6. Terminal disinfection: Airing the clothing.

"(B) *General measures:* None."

Curative Treatment.—Generally speaking, this is a very simple matter; little if any treatment is required in the majority of cases, as the child is not sick enough to go to bed. In the average case, a child should be confined to the house, the bowels should be opened with broken doses of **calomel** followed by a **saline.** The **diet** should be modified according to the severity of the case. **Water** should be taken freely at all times, and the body should be kept clean by a daily **bath.** Protect the skin by anointing daily with **carbolized vaselin** (**carbolic acid** drops 5 to **vaselin** 1 oz.) or **oil of eucalyptus** and **olive oil,** equal parts of each. During the three or four days of active symptoms in this disease, many clinicians are in the habit of using (especially in young children) **sulphate of quinin** disguised in chocolate syrup (strength grains ii or iii of quinin (0.13 to 0.2 grams) to a teaspoonful of syrup). Dosage is a teaspoonful every four hours. If the urine is scanty and red and there is pain in passage, the following prescription will be found beneficial:

℞

Sp. ætheris nitrosi	.............f ʒ ii (8 c.c.)
Potassii acetatis	.... ʒ ii (8 grams)
Lik. ammonii acetatis Aq. camphoræ	āā...........f ℥ iss (45 c.c.)

M. Ft. Sol. Sig.: Teaspoonful in water every four hours.

(Suitable for a child 4 to 8 years of age.)

For the treatment of special symptoms see similar heading under measles.

Prognosis.—The prognosis in this disease is, generally speaking, good. It is the simplest, and, from the standpoint of clinical manifestations, the mildest of the acute exanthematous diseases. Deaths in uncomplicated cases occur with extreme rarity. The simple character, mild symptoms and the short duration of the average case of rubella constitute one of its danger points. The child is not sick enough to go to bed; the eruption is fugitive, lasting only a day or so; the family in many instances do not call a physician to see the case, they make a diagnosis from other cases in the neighborhood. Such cases are not properly cared for; they are not put to bed, often not even confined to the house. They, perhaps, are allowed to play out of doors constantly and are exposed, get chilled, etc., and in about two weeks the family doctor is called. He finds that the child has an acute endocarditis, or otitis media or an acute parenchymatous nephritis. When the disease occurs in an epidemic form among poor and ignorant people who live amid unhygienic and unsanitary surroundings the prognosis increases in gravity and the mortality is correspondingly higher. The presence of severe complications and sequelæ increases the gravity of the prognosis. Some epidemics have been reported with a death rate of from 2 to 4 per cent.

Pathology.—This disease has no characteristic pathology. The eruption was fully described above, likewise the characteristic catarrhal processes which are prone to occur in the mucous membranes of the respiratory and gastro-intestinal tracts are analogous to those which occur in the same anatomical situation in rubeola, though as a rule they are much milder. They have received attention under the proper headings. The pathologic changes found present in complications and sequelæ do not *per se* belong to this disease. They are discussed elsewhere.

History.—The history of this disease is shrouded in confusion on every hand. There is hardly any disease concerning which the opinions of competent and careful clinicians show such a great degree of variance. Many have denied the very existence of this disease; others regard it as a form of attenuated measles, still others as an hybrid of measles and scarlet fever.

The epoch-making work of certain observers has given us a clean-cut, universally accepted clinical picture of measles and scarlet fever. No such results, however, have been attained in the case of rubella. Every symptom of the disease is subject to great variation. The rash, the strongest and most prominent symptom of the disease, is no exception to the above rule. In fact, the multiform character of the rash has always proven to be a universal stumbling-block. Certainly the type resembling measles (rubeola-form or morbilli-form type) is by all odds the commonest. The macular type (the spots varying in size from a pinhead to that of an adult finger-nail, and exhibiting a faded or old-rose color) may some day be distinguished as a separate disease. Dr. Clement Dukes, an English physician, in July, 1900, described what he called "the fourth disease." His views are noted by almost every writer, but accepted as proven by none. Bergen, a German physician, in 1752, was undoubtedly one of the first men to present the claims of this disease as a distinct entity. Sufficient grounds for establishing this as a fact is commonly accredited to Maton, an English physician, who, in 1815, pointed out the pertinent facts—that one attack of this disease furnished immunity; it did not, however, protect the individual from either scarlet fever or measles and, conversely, having had scarlet fever or measles or both, did not protect against this disease. Rubella occurs in epidemics, and, as is often the case under such circumstances, presents fairly constant characteristics. The name rubella (diminutive for rubeola) was first proposed by Veala in 1866. The Germans still give to this disease the name of rubeola. Among English-speaking peoples the correct scientific term for the disease under discussion is rubella.

CHAPTER XV

PAROTITIS EPIDEMICA

(*Mumps*)

By William A. Jenkins, A.M., M.D.

Definition, p. 311—Etiology, p. 311—Symptomatology, p. 312—Period of incubation, p. 312—Invasion, p. 313—Progress, p. 314—Anomalies or irregular types of mumps, p. 314—Consideration of special symptoms, p. 315—Laboratory findings, p. 317—Diagnosis, p. 317—Differential diagnosis, p. 318—Complications, p. 318—Sequelæ, p. 321—Treatment, p. 322—Prophylaxis, p. 322—Curative treatment, p. 323—Convalescence, p. 326—Prognosis, p. 326—Pathology, p. 326—History, p. 327.

Definition.—Parotitis epidemica is an acute specific infectious disease of unknown origin, characterized clinically by an involvement of the salivary glands, chiefly the parotid, and a tendency to invade glandular structures elsewhere in the body, especially the glands of the genital tract, notably the testes in the male.

Etiology.—(1) Predisposing Causes.—Cold, climate, season, altitude, soil and race seem to exert no influence whatever as predisposing factors.

Sex.—As a rule, most authors say that mumps is more frequent among males; we must remember, however, that most of our statistics are taken from male schools or from army barracks and camps. If we take a view of the disease in its entirety and consider epidemics everywhere, it is doubtful if we can substantiate this assertion.

Age.—Cases have been reported in which a child was born with mumps in an active stage, as, e.g., a case, where the mother developed mumps at the eighth month of pregnancy and her child, born at full term, had enlargement of the parotids and difficulty in swallowing. Instances of this sort are, of course, rare. The disease in this instance had been transmitted through the placental circulation. Mumps may be said to be rare under four years. The period from four to fifteen years is the most favorable time for this disease to appear. This is especially true in civil practice. Cases in young adults are fairly common in the epidemic form in schools and army camps, but relatively uncommon in civil life.

Mumps rarely attacks an individual past middle life; however, cases are occasionally reported. Heredity or family predisposition is never a factor. Fatigue, hardships and exposure, coupled with overcrowding and poor hygienic surroundings, generally all act by lowering resistance, and thus secondarily they become predisposing factors. One attack usually confers immunity, but cases are reported in which there were second or even third attacks. Relapses are uncommon, but do occasionally occur, as the literature of the subject will verify.

(2) EXCITING CAUSES.—We have every reason for placing this disease in the class of acute infectious diseases, for it is contagious or transmissible, it occurs in epidemics, it has an incubative interval, it has a definite clinical course, it is accompanied by fever and has possibly a blood-picture, a lymphocytosis, which is perhaps both relative and absolute.

The specific microörganism of this disease has never been isolated. Many workers have discovered organisms from the secretions of the mouth and from the blood or from punctures of the parotid glands, and have made the claim that the organism discovered by them was the specific organism of the disease. These reports are all lacking in confirmation. Numerous instances are to be found in the literature of the subject where the secretions of the mouth, taken from a subject suffering from mumps, were filtered and the filtrate used to inoculate lower animals, for example, the cat, with the result that an inflammatory process occurred in the parotids, followed even by atrophy of the testicle. Work of this character may serve to verify the transmissibility or contagiousness of this disease, but has not thus far thrown any light on the specific organism. The organism is certainly in the blood, but is most commonly supposed to abound in the secretions of the mouth, throat and likely the nose. The chief method of conveyance of this disease is certainly by direct contact from patient to patient. An individual who comes in contact with a case and handles articles soiled by the patient may carry the disease to others, without taking it himself.

Finally, it is more than likely that bed-clothing, towels, handkerchiefs, etc., soiled by an individual having mumps may retain organisms for a variable period (ten to twenty days), and thus furnish opportunities for infecting other individuals. The original infection in all probability gains entrance into the system through the nose; then it either becomes admixed with the secretions of the mouth, and travels directly up the ducts of the salivary glands (e.g., Steno's duct to the parotid), or, which is more probable, it is first taken into the general circulation and is later by this means carried to the salivary glands as the tissue of special predilection.

Symptomatology.—PERIOD OF INCUBATION.—It is commonly conceded that the incubative interval of this disease is quite long as compared to the same interval in the exanthematous diseases, for instance. Some of the factors, brought forward by competent and experienced observers, which may be taken into consideration as throwing some light on the confusing statements regarding the true limits of this period, are as follows:

(1) The possibility of a long pre-incubative interval. The causative organism may gain entrance into the body, but may be held up in a location unfavorable to growth for quite an appreciable period of time.

after which it may be transported to its particular selective tissue, where growth really begins.

(2) The prodromal or invasional period of this disease is definitely known to be exceedingly variable; some authors report well authenticated cases, too numerous to be overlooked, in which definite prodromes were noted for a week before the enlargement of the parotid gland appeared. Other competent observers give it as their opinion that at least twenty-four to forty-eight hours of mild prodromal symptoms is the rule, while still others appear to regard prodromal signs as the exception. These latter observers count the enlargement of the parotid gland as the beginning of symptoms.

(3) The life-cycle of the specific organism of mumps may be an unusually long one; this possible explanation of the long incubation in this disease must certainly be given due consideration, as it meets most of the needs of the problem to a nicety.

(4) It is to be borne in mind that microörganisms, generally speaking, gain in virulence under favorable conditions of growth, and that, conversely, under unfavorable conditions they tend to lose in virulence, or become attenuated. Any of the above factors may play a part in the determination of the time-limits of the incubative interval of mumps. The causative organism has never been isolated; therefore, we cannot make cultural experiments. Artificial inoculations, in the human species, at least, have not been successful; hence we cannot try out or verify any of the above statements. Some clinicians report cases with an incubative interval as short as four days; others say the minimum period is eight days; again, cases believed to be authentic are reported in which the incubative interval was as long as thirty days. A child in the initial stages of mumps—before the diagnosis is made—may be admitted into an orphan asylum or children's hospital, and after the child has mingled freely with the other children his parotid gland may enlarge; he has fever and a diagnosis of mumps is made. We may now observe the exposed children for the first symptoms of mumps. Usually the first case (or cases) develops in approximately fourteen to twenty days; the above method of clinical observation is at the present time the only reliable means at our command from which we may draw conclusions as to the time-limit of this period. From a clinical standpoint, then, we say with a fair degree of certainty that the time-limit of the incubative interval of mumps is from two to three weeks (fourteen to twenty-one days).

INVASION.—In the average case of this disease, we have a fairly characteristic group of invasional symptoms: usually chilly sensations and restlessness for about two days, and very commonly aching pains about the joints and limbs. The throat feels dry and sore; some temperature is noted at this time, usually 99°-100° F. (37.2°-37.8° C.) (occasionally running as high as 102° or 103° F. [38.9° or 39.4° C.]); loss of appetite is almost universal, and gastric irritation, nausea and vomiting may be present. After about forty-eight hours of the above symptoms, pain is complained of in one or the other of the parotid regions; slight swelling is now noticed in the affected parotid gland; deglutition or swallowing becomes difficult; the patient does not like to talk or open the mouth wide. Oftentimes at about this time considerable pain in the ear is complained of. The disease may now be considered to be definitely developed.

Progress.—The affected parotid—either the right or the left; there is no definite predilection for the process to begin in one side or the other —becomes markedly enlarged, usually filling up the space immediately below the ear between the ascending ramus of the inferior maxillary bone and the mastoid process. The gland becomes much enlarged and the subcutaneous structures in the immediate neighborhood become involved. (Occasionally the submaxillary gland enlarges at the same time.) The patient now presents a very characteristic and oftentimes grotesque appearance, this being especially true if both sides are involved at the same time. The facial appearance is so changed that the individual may be unrecognizable. The malaise and slight aching of the joints and limbs remain and often become intensified; the child is hardly able to swallow or even open the jaws; the mouth is usually dry.

The fever continues—100°-103° F. (37.8°-39.4° C.) as a rule; the glandular swelling usually reaches its height in about three or four days, lasting altogether about five to ten days. Very commonly, as the swelling begins to subside, the opposite parotid begins to pain or show some swelling, and in turn passes through the same stages as the gland first involved. The overlying skin often has a tense, glazed appearance and the parotid has a doughy feeling, or it may be very hard. The tissues overlying the involved parotid may be entirely normal in appearance. Clinically speaking, in the average or type case of mumps, the order of the glandular involvement is about as follows: First and most commonly, we have the involvement of first one parotid and then the other. Generally the second gland becomes involved about the time the first one begins to subside. (Sometimes, but more rarely, the inflammatory process in the first gland disappears entirely and there is an interval of quiescence of four or five days before the second gland becomes involved.) Second, both glands may be involved at the same time, giving the patient a grotesque and unrecognizable appearance, as mentioned above. Third, the disease may develop on one side only, when only one parotid gland becomes involved throughout the course of the disease. Very often the whole disease process may be over in four or five days, or it may last for ten days or two weeks. With the disappearance of the enlargement of the parotids, in a typical case, all the other symptoms subside and the patient gets well promptly.

The above description will fit fairly well the average case of mumps. Let us now turn our attention to some of the anomalies or irregularities of this disease.

Anomalies or Irregular Types of Mumps.—(1) *Mild or Abortive Type.*—The mild or abortive type is one in which not only prodromal but even general or systemic symptoms are either absent or are so mild that they pass unnoticed. The patient is not ill, the enlargement of the parotid being the only symptom that makes known the presence of the disease. And even this is not marked and passes away quickly (three or four days) without leaving any traces behind. Cases belonging to this type are sometimes so mild that diagnosis would be doubtful or impossible if the cases occurred sporadically. When, however, these cases occur during epidemics the diagnosis is easy.

(2) *Severe Type.*—The severe type is one in which the individual may be prostrated from the start—with temperature high, heart weak and a low typhoid-like state. Some such cases have been reported as occurring in epidemics by Army medical men. They are never very common.

(3) *Systemic Type.*—Next we have the type in which there are marked systemic symptoms and no inflammation of the parotids whatsoever. Some of the other glands of the salivary group may be involved, for example, the submaxillary or the sublingual; or some of the glands of the genital tract also may be involved, namely, the testes in the male. Some of these cases likewise present diagnostic difficulties. When they occur in the midst of an epidemic the diagnosis is easy; when they occur sporadically great care must be exercised in making a diagnosis.

(4) *Relapsing Type.*—The relapsing type is one in which one group or set of glands is involved at a time—e.g., the parotid and submaxillary or the sublingual group, etc.—with an interval between the attacks; general symptoms accompany each attack, and complications may occur with any one of them. In this connection it may be of interest to quote an instance which very beautifully illustrates the above type. The case in question occurred under the observation of a physician by the name of Karth, and is reported by Jules Comby * as follows:

"In a patient under the care of Karth there were no less than five distinct attacks, each one marked by fever and general symptoms. The first attack, which was the gravest of all, affected the salivary glands, the kidneys and the spleen; the second involved the lacrimal glands; the third, limited to the parotids, enabled a diagnosis of mumps to be made; the fourth was marked by a swelling of the submaxillary glands; in the fifth attack the lacrimal glands were alone attacked. Each successive attack in this series was less grave than its predecessor."

Those of us who see quite a bit of this class of work can bear witness to the fact that relapses do occur in this disease.

(5) *Chronic Type.*—In this form the parotid glands remain chronically enlarged for weeks or even months after the general symptoms subside. Some slight local manifestations or symptoms may, however, accompany the enlarged glands for quite a long time.

CONSIDERATION OF SPECIAL SYMPTOMS.—The prominent or leading symptoms of the disease are subject to such variations that it seems best just at this point to discuss them *seriatim.*

(1) ***Characteristic Enlargement of the Salivary Glands.***—The par-

---

* Jules Comby on "Mumps," "Twentieth Century Practice of Medicine," Vol XIII, p. 577.

otid is the chief gland to be enlarged. It is the most important, the most prominent, and likewise the most frequent and dependable symptom of the disease. In mild cases it is the first symptom to be noted. Usually, first one gland is involved, and as it subsides the other gland becomes swollen. Occasionally both sides are involved at once, and still less frequently only one side is involved throughout the disease. The swelling may be very mild, and again in other cases it may be very marked. A special cutaneous edema appears in the neighborhood of the parotids; often the other salivary glands—the submaxillary and the sublingual—may participate. Now and then the submaxillary or the sublingual alone is involved, proved by the fact that the case occurs in an epidemic and may be accompanied by recognizable complications, namely, the involvement of the testes in the male. Although the whole neck may be much enlarged, as a rule we can readily make out the special salivary glands involved by palpation. Most commonly the skin and superficial tissues are loose and move freely over the gland; occasionally the skin is red, tense and shiny and perfectly tight. The pain and discomfort experienced by the patient are in direct proportion to the amount and character of the swelling. In extreme cases the suffering is great; the slightest touch causes pain; it is very difficult to open the mouth or to swallow, and severe earache is sometimes complained of. On attempting to open the mouth, a tetanic contraction of the masticatory muscles is sometimes present. The lymphatic glands about the neck may become enlarged. The involvement of the salivary glands subsides, as a rule, in about one or two weeks; occasionally it may last longer.

Secondary infection of the involved gland with the formation of pus (suppuration) is a remote possibility.

(2) *The Mucous Membrane of the Mouth and the Salivary Secretions.*—(*a*) *The mucous membrane of the mouth* in the average case is perhaps dry and redder than usual, and that is about all. In other cases the tongue and mucous membranes are much swollen; the gums are swollen, soft and boggy. The region of the orifice of Steno's duct is infiltrated and stands out plainly; the whole of the pharyngeal ring may be engorged and covered by a slimy secretion. Some authors claim that a characteristic enanthem is present in this disease. This view, however, is not accepted by experienced observers. Stomatitis or even tonsillitis may occasionally be present.

(*b*) Authors differ much in their statements regarding *the state of the salivary secretions,* but it may be stated as a clinically accepted dictum that, in far the greater percentage of cases, the flow of the salivary secretion is much decreased throughout the active period of the disease. The mouth and throat remain sufficiently dry to cause the patient great discomfort. The secretions tend to become normal in quantity as the glandular involvement subsides. Sometimes in convalescence a troublesome hypersecretion is present for a considerable time. Very rarely one encounters a case which is marked by hypersecretion during the active stage of the disease, such cases not being common.

(3) *Constitutional Symptoms.*—In a great many cases, oftentimes even in epidemics, constitutional or general symptoms are so mild that they are said to be absent; their very mildness causes them to be overlooked. But some constitutional symptoms are always present, no matter how mild the case. The most constant and dependable constitutional symptom is fever. In every case in which there is sufficient parotid or other glandular involvement to justify the diagnosis, there is some fever present during the most active stage of the disease. This fever has no characteristic or diagnostic curve; it corresponds with and is directly proportionate to the character and type of the infection. In addition to the fever, we have very commonly, malaise, mild gastro-intestinal disturbance, aching and pains in the joints and limbs (very characteristic and oftentimes lasting several days). Tinnitus aurium, earache, marked pharyngitis and epistaxis are factors which may add themselves to our symptom-group in almost any case.

Finally we have quite a respectable percentage of cases in which the systemic symptoms are marked and even grave from the start.

LABORATORY FINDINGS.—Many authors place great stress on the blood findings in mumps. In the majority of cases we have a slight leukocytosis. The value of this point is somewhat negated by the following facts: (*a*) the leukocytosis is so slight that it is a question whether it constitutes a leukocytosis or not; and (*b*) the age at which mumps is most common—from four to fifteen years (childhood)—is a period in which the white cell-count runs much higher normally than it does in the adult. The question naturally then arises, Is it a leukocytosis? Secondarily, we have a lymphocytosis which is always relative, and in most instances absolute; further, this finding may be said to be present in all cases throughout the active stages of the disease. Relative lymphocytosis, however, is said by competent authors to be present in several of the infectious diseases of childhood: for example, in anemia, pertussis, bronchopneumonia, measles, etc. Blood-findings, therefore, have very little practical value in this disease. Perhaps, if fever is present and it is a question of differentiating an enlarged parotid gland of mumps from some acute inflammatory condition, such as pus in the gland, the blood-count may help somewhat.

A lymphocytosis of the cerebrospinal fluid is found where we have a meningitis due to mumps, as is noted elsewhere.

Diagnosis.—The diagnosis in the average or "type case" of mumps is easy. The typical enlargement of the parotid gland (most commonly unilateral) presents a characteristic appearance on inspection, and the anatomical outlines of the gland are readily made out on palpation. There is dryness of the mouth and difficulty in mastication and deglutition. The duration of the glandular involvement is relatively short; the swelling comes on quickly and as quickly subsides in from seven to ten days. The above picture, with few symptoms either preceding or following the glandular enlargement, is at once both characteristic and diagnostic. In irregular or atypical cases, the diagnosis is more difficult. This is especially true where the parotid glands are not involved; perhaps submaxillary enlargement alone is present, or, still more rarely, only the sublingual gland is involved. In the case of the submaxillary or the sublingual enlargement, if prodromal and systemic symptoms are present, and possibly even typical complications, we are able to approach the problem with more certainty.

If the above class of cases occur in the midst of an epidemic, our difficulty is very appreciably lessened. Occurring sporadically or in isolated instances, the above types might be impossible of diagnosis at all. In those very rare cases occasionally reported, where we have systemic symptoms and an orchitis (the salivary glands remaining entirely free), diagnosis is impossible without, and exceedingly hazardous with, the presence of an epidemic. We occasionally see, most commonly in epidemics, cases with grave systemic symptoms from the very start, prostration marked, and the typical glandular symptoms absent or delayed. Diagnosis here is, of course, a matter of great difficulty. The type-symptoms may come out more plainly as the disease progresses. Fortunately such cases are rare.

DIFFERENTIAL DIAGNOSIS.—It should always be borne in mind that the parotids and likewise the other salivary glands may be enlarged from causes other than mumps; for example, non-specific parotitis, due to irritation of some type, such as acute iodism. Again these structures are frequently involved secondarily by infectious microörganisms, the specific type of parotitis. Enlargements in the neighborhood of the parotids (which look like mumps) may be present in tonsillitis or diphtheria; likewise periauricular or cervical lymphadenitis may cause some confusion. In making the differential diagnosis, in addition to the local examination, one should always examine the mouth and throat. A careful history of the case should be obtained and a complete physical examination made before conclusions are drawn.

Complications.—IN THE MALE.—Involvement of the structures of the genital tract is by far the commonest type of complication in mumps, and of these structures the testes seem to be the point of special localization. *Orchitis* is rare in children. It is quite uncommon for this condition to be found under fifteen years of age. On the other hand, it is quite common in young adults (after the genital organs are fully developed) and in certain instances where young adults are crowded together, with the elements of exposure and physical fatigue, for example, army barracks and camps, the percentage of orchitis runs very high. Some observers give statistics of epidemics among adult males in which the percentage of orchitis ran as high as 25 to 50 per cent., while others place the average at about one case in every fifteen of the disease. The onset of the orchitis is in most instances marked by (1) sharp and sometimes grave symptoms, for example, high sudden rise of temperature, restlessness and delirium, the affected testicle being much enlarged, heavy, red and painful, with pain running along the course of the spermatic cord. (2) Again it may come on insidiously with slight or no pain, simply an enlargement of the testicle. The whole testicle is enlarged; the parenchyma of the gland shows the greatest involvement, and, generally speaking, the epididymis is involved also, though to a less extent, the process being in most cases an epididymo-orchitis. This complication usually shows itself in from five to eight days after the onset of symptoms, or, in other words, as the primary point of involvement, the parotid, is subsiding. This is so common that most authors speak of the process as a *metastasis*, i.e., the disease seems to be leaving one part to invade another. In other instances there may be a period of a few days after the parotid swelling goes down before the testicle becomes involved. As a rule, the acute inflammation of the testicle subsides in about three to five days, although some swelling and tenderness on manipulation may remain throughout convalescence or even longer. (3) Finally, as was mentioned under Anomalies or Irregular Types of Mumps, the orchitis may show before the parotid swelling has subsided, or even before its involvement, or without any discoverable manifestations in the salivary glands at all. In this last instance the diagnosis can be made only where systemic symptoms were present and the case occurs in the midst of an epidemic. The above irregularities are possible but not probable. (4) Secondary infection and consequent suppuration may occur in the orchitis of mumps, and such a case is occasionally noted in the literature. The seminal vesicles are quite often involved to a varying extent. Marked tenderness may be noted along their course on examination per rectum. At the same time the prostate may be found to be enlarged and tender; urethral irritation may be present. Cases of non-specific urethritis (no gonococci found) have rarely been reported.

COMPLICATIONS IN THE FEMALE.—In the female the *ovaries* may be involved. This complication, however, is not nearly as common as an orchitis in the male. When ovaritis does occur, it is much less intense than the analogous process in the male. The time of appearance and disappearance of this complication bears the same relationship to the inflammatory process in the parotids as the orchitis does in the male. *Inflammation about the labia* is reported as occurring in rare instances. *Mastitis* or enlargement of the mammary glands has been reported by a large number of observers. It is possible for this complication to occur in either sex; it is much more likely, however, to appear in the female. *Thyroid enlargement* is occasionally noted; it usually subsides in from a few days to two weeks. It is most likely due to toxemia. Enlargement of the lymph glands, *cervical lymphadenitis*, appears to be fairly common. It is always secondary and as a rule does not last long; it may be regarded as an expression of systemic toxemia. *Suppurative parotitis* is a complication which is possible but rarely occurs. One observer with several thousand cases to his credit saw suppuration appear but twice.

GENERAL COMPLICATIONS.—*Acute Pancreatitis.*—Epigastric pain, vomiting and tenderness in the region of the pancreas, with diarrhea and fever, is a symptom-group which has caused the diagnosis of pancreatitis as a complication to be made many times. That such an event does occasionally occur there can be no reasonable doubt, for the cases seem well authenticated. It is very likely, however, that many of the cases reported were undoubtedly instances of acute gastric irritation, as part and parcel of the symptom-group in an acute infectious disease.

Mouth and Pharynx.—Stomatitis and sore throat are not infrequent.

The Respiratory Tract.—Complications here are not frequent—edema of the glottis, bronchitis and even bronchopneumonia have been occasionally reported.

Arthritis.—Severe, aching pains about the joints, without the clinical evidence of inflammation, which persist for several days are often present, and are erroneously called "rheumatism." They are simply toxic manifestations of the disease. This manifestation, milder in degree and of shorter duration, occurs in the majority of our cases, as stated above under the head of Symptoms.

The Heart.—The heart is rarely involved in this disease; temporary functional disturbances may arise, but they disappear as the disease subsides. Very rarely, severe cases in epidemics may develop pericarditis or endocarditis.

The Kidneys.—Albuminuria, especially in the moderately severe cases, is quite common—according to some authors, 15 to 20 per cent. Hematuria is reported. Acute nephritis occurs occasionally.

The Nervous System.—Functional disturbances of the nervous system often accompany other complications, e.g., restlessness and delirium with orchitis. In the severe form of the disease, marked toxic effects are produced on the nervous system. Mania, sudden and furious, aphasia, monoplegia and hemiplegia or other types of disturbance are occasionally noted under the circumstances mentioned above. Paralysis of various types occasionally occurs, for example, an inferior paraplegia accompanied by paresthesia and formication. Neuritis occurs in single nerve-trunks or related groups of nerves; even multiple neuritis is encountered now and then.

Owing to its passage through the parotid gland, involvement of the facial nerve is not at all uncommon. Disturbance of the optic and auditory mechanism occasionally occurs.

The nervous system is particularly liable to be involved in grave cases, especially where complications are marked and severe; for example, where the complication of orchitis comes on in a stormy manner, with high temperature, we are very likely to have great restlessness, accompanied by active delirium. *Meningitis* is occasionally seen in almost every great epidemic. This is especially true of mumps in barracks or camps. Sudden deafness may appear at any time in the course of the disease; it may be accompanied by noises in the ear (tinnitus), vomiting, vertigo, etc., or it may appear without other symptoms. Sometimes the deafness disappears; again, unfortunately, it is permanent. No adequate explanation is at hand to account for this sudden deafness. In the majority of the instances of involvement of the nervous system (including even the severe forms mentioned above) ultimate recovery finally takes place; it may take weeks or even months, however, to accomplish this. In a small percentage of cases the damage is permanent and may result in the death of the patient.

Sequelæ.—Any severe single symptom or any complication which persists, or remains after the manifestations of the disease proper have disappeared, should, strictly speaking, constitute or be spoken of as a sequel. From a strict clinical standpoint, however, it would be best to place in this class only those conditions which follow or come on after, or are the end-result of severe symptoms and complications (*sequor,* Latin, meaning "to follow").

SEQUELÆ OF THE GENITAL TRACT.—*Testicular atrophy* is an important and fairly common sequel of mumps. Orchitis appears towards the end of the period of parotid swelling, attains a maximum point and subsides usually in about three to five days. Pain, edema and inflammation disappear (some enlargement remains for a time, perhaps a few weeks), the patient is declared well, no further observations are made on him and perhaps some months later, when his physician is examining him for life insurance, the testicle is found to have undergone atrophy. Occasionally the patient comes to his doctor voluntarily and says that the testicle in which he had the mumps has "shrunk." Atrophy is not noticed because it progresses very slowly and there are no active symptoms. The atrophy begins, perhaps, in about two months after primary involvement and may continue for as long as one year. The atrophy varies in degree; the organ may be decreased in size, one-fourth to one-half, or it may be reduced to the size of a large bean, being very hard and insensible to pressure. Rarely the gland softens, and still more rarely it remains permanently hypertrophied. The amount of damage done depends on (*a*) the amount of testicular atrophy and (*b*) whether one or both testicles are involved. In the majority of instances the enlarged gland is rendered impotent and sterile and, if both glands are involved, the affected individual may be incapable of reproducing his kind, though the desire and the ability to perform the sexual act may remain normal, depending upon the degree of atrophy. Where atrophy is double and complete, practically all of the gland-substance being destroyed, at least so far as function is concerned, the so-called internal secretion is absent, and the affected individual may show some of the characteristics of effeminacy, e.g., the eunuch-voice, enlarged mammæ, rotundity of figure, etc. This latter fortunately is exceedingly uncommon. Rarely, the atrophied testicle may undergo suppuration. Likewise the *prostatic gland* may atrophy, following mumps. If these phases of the subject were looked into more thoroughly and examinations made more frequently, more cases would be reported. (We have no sequelæ, so far as is known, in connection with the glands of the female genital organs analogous to those described above in the male.) Some hypertrophy of the salivary glands, or even the cervical lymphatics, may remain as a sequel of the mumps.

GENERAL SEQUELÆ.—*The Kidneys.*—True nephritis occasionally occurs as a sequel of this disease.

The Heart.—This organ is rarely involved. Endo-, peri- or myocarditis are remote possibilities. Cases are occasionally reported.

The Nervous System.—Certain forms of spinal or peripheral paralyses, such as were mentioned under Complications, may occur as sequelæ. The conditions usually clear up completely in time, although occasionally some weakness and intermittent paresthesias may persist for years or throughout life. As mentioned under Complications, permanent deafness is sometimes noted.

Treatment.—PROPHYLAXIS.—Experience in epidemic work teaches us that this disease is a readily transmissible one. We have every reason to believe that the causative agent is a filterable virus. We are quite sure that the disease is transmitted chiefly by the secretions from the mouth, throat and nose of the diseased individual. The organism is certainly in the blood. It is a fairly safe conclusion, however, that it is chiefly the secretions of the mouth, nose and throat that we have to watch particularly. The mode of transmission is most commonly direct from person to person. We know, however, that it is transmitted indirectly through articles, clothing or fomites recently soiled with the secretions and discharges mentioned above. It is probable that the organisms do not live longer than about ten to twenty days on soiled articles or fomites. The disease is communicable from the very earliest symptom (or even before that) until the time when all traces of enlargement of the parotid glands have disappeared and the leading symptoms have all abated.

With the above as a summation of our actual knowledge regarding the causative agent, its method of transmission and its period of communicability, we may formulate methods of control which will apply to the individual himself and likewise to the community in which he is located. The methods commonly used to prevent the spread of acute infectious diseases are, in general, about the same everywhere. We can do no better than accept the rules laid down for the control of communicable diseases as contained in the report of the American Public Health Association Committee on Standard Regulations, printed in October, 1916. They are as follows:

"METHODS OF CONTROL

"(A) *The infected individual and his environment:*

"1. Recognition of the disease: Inflammation of Steno's duct may be of assistance in recognizing the early stage of the disease. The diagnosis is usually made on swelling of the parotid gland.

"2. Isolation: Separation of the patient from non-immune children and exclusion of the patient from school and public places for the period of presumed infectivity.

"3. Immunization: None.

"4. Quarantine: Limited to exclusion of non-immune children from school and public gatherings for twenty-one days after last exposure to a recognized case.

"5. Concurrent disinfection: All articles soiled with the discharges from the nose and throat of the patient.

"6. Terminal disinfection: None.

"(B) *General Measures:* None."

Curative Treatment.—Treatment consists of: *first,* general management, including the treatment applicable to the average case; *second,* treatment of special symptoms, complications and sequelæ.

(1) *General Management and Treatment of the Average Case.*—In a large percentage of the cases occurring in private practice, the disease is so mild that the patient suffers no inconvenience whatever and little or no treatment is required. Even mild cases should be confined to the house for the active period of the disease (say ten days to two weeks) and if fever is present the case should be confined to bed during the active stage of the disease. The bowels should be cleaned out at the start with **calomel (alone or combined with rhubarb and soda or phenolphthalein)** in broken doses or in a single dose, depending on circumstances and the preference of the attending physician. A few hours after the calomel, **castor oil** or **salines** should be given. The bowels should be kept well open throughout the acute phase of the disease. The **diet** should consist of articles that are easily handled or digested, which should be in the form of liquids or semi-solids, as on account of the swelling and pain it is usually difficult for the patient to open the mouth or swallow. The body should be kept clean by a daily cleansing bath—an ordinary **tub-bath** when not confined to bed, and a **sponge-bath** if so confined. The nose, mouth and throat should be carefully looked after throughout the attack; the mouth should be washed out carefully with plain water after each feeding. About every four hours the nose and throat should be sprayed out with some suitable antiseptic, e.g., **boric acid** 5 per cent., **carbolic acid** 1 per cent., or **chlorazene** 1-1000 to 1-500. (The above measure serves the double purpose of acting as a check on the spread of the disease, and keeping down complications such as stomatitis, tonsillitis, etc., in the individual case.)

Fever.—In the acute phase of the average case, barring complications, fever is not likely to be sufficiently high to demand special treatment; when it is high at this stage, **brisk purgation** and **hydrotherapy** meet the needs of the case as a rule. Occasionally, when the glandular swelling is at its height, the throat quite dry and sore, the patient restless and uncomfortable, with a moderately high fever of 103° or 104° F. (39.4° or 40° C.), a dose or two of the following will be found useful as an emergency remedy:

℞

Acetphenetidini	grains iii (0.20 gram)
Caffeinæ citratis	grains ss (0.03 gram)

M. Ft. Caps. No. 1, Sig.: One such capsule every three hours.

(For children from 4 to 12 years of age.)

Usually after about the second dose the temperature drops, restlessness disappears, the patient feels more comfortable and may go off to sleep. Aching pains about the joints and limbs are quite frequently complained of; they may occur at any time throughout the active period of the disease, or even as the symptoms begin to decline. This symptom is often quite troublesome, and it seems to respond quite well to the salicylate group of drugs, e.g.:

℞
Acidi acetyl-salicylici, tablets, grains v (0.325 gram)
Sig.: One every four hours (for a child 10 years or over.)

Or the following may be used:

℞
Sodii salicylatis }
Sodii bicarbonatis } āā..........ʒ iii (12.0 grams)
Aq. gaultheriæ ....f ℥ iii (90.0 c.c.)
M. Ft. Sol. Sig.: One teaspoonful in cold water every four hours.

Local Treatment of the Inflamed Glands.—In many instances no treatment is necessary. If, however, much pain is complained of locally, some form of treatment may be instituted. Several layers of absorbent cotton may be placed over the inflamed gland and retained in place by a bandage or cloth bound over the head. Hot compresses, or even a hot-water bottle or electric pad, are occasionally used. In some instances the opposite extreme, cold applications, seem best, such as the use of ice-water cloths, cold packs or the ice bag.

The Use of Drugs as a Local Treatment.—As a local application for use on the inflamed gland, the following prescription may be found useful:

℞
Ung. belladonnæ }
Ung. hydrargyri } āā................f ℥ i (30.0 c.c.)
M. Ft. Ung. Sig.: Apply locally, as directed.

The above ointment is to be spread freely on a piece of cheesecloth, and placed on the gland. Apply some absorbent cotton over this. The whole is retained in place by a bandage or cloth bound around the head.

(2) *Treatment of Special Symptoms, Complications and Sequelæ.*—The treatment of markedly inflamed and painful enlargements of the parotids is outlined above. The special measures applicable to fever are likewise given above.

Orchitis.—The best method of treatment of this complication is the *prevention* of its occurrence. In any case of mumps occurring in an adult (from about seventeen years and over) where the disease is at all severe and is complicated by fever, the patient should be put to bed at once and kept there throughout the active phase of the disease. This measure will minimize the likelihood of orchitis very considerably. If this complication has already occurred, or occurs in spite of our best precautionary efforts, more active measures must be promptly instituted. The bowels should be opened thoroughly and kept open as long as this complication is present. The diet must be reduced to liquids, preferably milk. Water should be taken freely. For the fever use **acetphenetidini,** grains iii or v (0.2 or 0.3 gram) every three or four hours for three or four doses. If this remedy (or some of its congeners) is not effective by this time, it should be promptly dropped, and chief reliance should then be placed on **hydrotherapy.** For the active delirium which is prone to occur with the onset of this complication, the best single remedy is **gelsemium.** (Use whenever possible a properly assayed, physiologically tested, time-limited preparation of this drug, in other words, an active preparation.) The dose should be small and frequently repeated up to physiological effect, namely, the quieting of the patient and the disappearance of the delirium. Some authors favor the use of the **bromids** for the delirium, either **sodium or potassium bromid,** dose suitable to the age of the patient, say ten or fifteen grains every four hours (for age seventeen or over).

Local Treatment as Applied to the Inflamed Testicle.—**Guaiacol** is undoubtedly the best single remedy; 10 to 20 per cent. in glycerin is to be applied freely to the inflamed gland. A nest of absorbent cotton is next fitted snugly around the inflamed organ and the whole kept in place by a loose-fitting suspensory bandage or adhesive strips properly applied to obtain rest and relief from dragging on the cord. The above plan usually meets the indications very nicely, and the swelling subsides ordinarily in from three to five days. Occasionally it may last longer.

The *meningeal irritation* or *meningismus,* as it is now popularly called, which is prone to occur in severe cases during the active or febrile stage, is sometimes a sudden and alarming symptom. In addition to thorough purging, **hydrotherapy** and other general measures as indicated. The above condition is combated by the use of **gelsemium** as directed above, or as some authors prefer, by a combination of **bromids** and **chloral hydrate,** for example:

℞

Potassii bromidi	℥ ss	(15 grams)
Chlorali hydrati	ʒ iii	(12 grams)
Aq. menthæ piperitæ ....f	℥ iii	(90 c.c.)

M. Ft. Sol. Sig.: Teaspoonful every four hours.

Occasionally it will be necessary to administer **morphin,** grains ¼, and **atrophin,** grains 1/150, hypodermically for one to two doses. This will usually carry the patient safely through the above described complication. Fortunately, this complication does not last, as a rule, over three to five days in an acute form. If we have a true inflammatory process of the meninges, however, the story is quite different. True mumps meningitis does occasionally (though rarely) occur. The majority of the cases in the literature are reported by military surgeons as occurring among soldiers. The mortality is very high in these cases, and the treatment applicable will be found under the subject of Meningitis. The treatment of the rare complications and sequelæ of this disease does not, strictly speaking, belong to the average textbook picture of this disease; should they arise, however, their treatment would be along the lines indicated by the particular type of complication or sequelæ, and the circumstances attending thereon.

CONVALESCENCE.—This period in the average case is uneventful; occasionally it may be rather prolonged. The patient is pale and seems to be weak, regaining strength slowly. A particular reason for regarding this period as of some importance is the fact that it is a period of possibilities. The patient is naturally susceptible at this time. The illness was slight, therefore the patient did not take proper care of himself, and exposure and over-exertion invite complications. It, therefore, seems well just at this point to sound a note of warning. Physicians in general should at least supervise the patient throughout this period. It seems to the writer that the convalescent period in all infectious diseases does not receive the attention that it merits from the medical profession. Although all active symptoms of disease may have disappeared and the patient may express himself as feeling well, there is still danger and the patient should be under the observation of the physician for reasons that are obvious. In the severe or grave forms, the period of convalescence will be prolonged in proportion and may be more stormy in character.

Prognosis.—The prognosis, generally speaking, is good; the mortality in this disease is exceedingly low. In uncomplicated cases, no deaths are reported. A death occasionally occurs from some serious complication, e.g., meningitis. In spite of the fact that the mortality is low and the disease usually mild, our experience teaches us that an individual ill with mumps is subject to considerable inconvenience, but of far greater importance is the fact that this is a disease of possibilities. Complications and sequelæ are fairly common, especially in epidemics, and complications and sequelæ may impair or cripple the usefulness of the affected individual temporarily or even permanently.

Pathology.—Our definite knowledge of this phase of the subject is meager. As is agreed by most authors (and verified by the statistics), opportunities for postmortem work are rare. The disease is often crippling but seldom fatal. When death does occur, it is usually due to some complication which is so severe that it masks or obliterates the primary changes. So far as we now know, in mumps proper, excluding complications, the pathology is found chiefly in the salivary glands. The microörganism is supposed to enter the salivary ducts from the mouth, though it may come through the blood stream, and make its way to the gland-substance. The gland-ducts and gland-substance would then most likely be involved first, and the periglandular tissue secondarily. There is, perhaps, swelling and hyperemia of the walls and linings of the ducts, and likewise of the acini of the glands. The swelling is sometimes so great that the ducts of the affected glands are occluded. (In the case of the parotid gland, Steno's duct may be readily felt with the fingers as a firm cord-like structure.) The periglandular tissue is likewise swollen and inflamed, even edematous, and round-celled infiltration most undoubtedly takes place; no true hypertrophy, however, is supposed to occur. In simple cases nature is usually able to bring about a condition of *restitutio ad integrum.*

The above is approximately the full extent of the pathologic changes in the acute or active stage of the disease. As an end-result we may have an hyperplasia of the parotids which may not clear up for months.

The end-result of the testicular involvement is, as a rule, a parenchymatous sclerosis of the testicle combined with atrophic changes. The pathologic changes, accompanying severe complications and sequelæ, are not, strictly speaking, a part of the pathology of mumps, consequently we shall not discuss them here.

History.—Medical historians inform us that the disease, mumps, was known in ancient times. The venerable Hippocrates, born 460 years before Christ, has left us a description of this disease which is unmistakable. After Hippocrates, clinical knowledge of this disease seems to have been swallowed up in oblivion for over two thousand years. We next find traces of it perhaps in the latter half of the seventeenth century and the first quarter of the eighteenth century (A. D. 1650 to 1725). The writings of various medical observers of the period mentioned above convince us beyond the shadow of a doubt that these men did see *bona fide* cases of mumps, and we are just as thoroughly convinced, from these same writings, that the aforesaid observers did not recognize the phenomena as a distinct disease. In truth, the enlarged parotids were confused with such conditions as the adenitis accompanying ulcerative stomatitis, tonsillitis, diphtheria and other conditions which would produce an adenitis or other type of enlargement about the neck. The subject of mumps during the above period was inextricably entangled in a confused mass, with many of the still undifferentiated acute epidemic infectious diseases. Authors are agreed that Hamilton, an observer of the epidemics of Scotland in 1761, did much towards bringing this disease out of its obscurity. This observer likewise noted the appearance of orchitis as a complication, and to Mangor (epidemic of Wiborg, 1773) is usually given the credit of recognizing mumps as an infectious disease. The study of the epidemics which occurred in Italy about this same period did much to clear up the situation, namely, the epidemic at Florence in 1752, observed by Targioni Tozzetti, and one at Bologna in 1753, observed by Laghi, and the epidemic which occurred in Genoa in 1752. We may safely conclude that the identity of mumps as a distinct disease was established, roughly speaking, about the middle of the eighteenth century (1750). It was recognized definitely as an infectious disease, and was known to occur in epidemic form; likewise its chief clinical characteristics and its more common complications were noted and accurately described. Mumps seems to defy all seasonal and geographical limitations; it is a disease which has occurred in epidemic form in almost every country of the civilized world; it is very prone to become epidemic where large numbers of young men are congregated together, for example, in schools and among troops in barracks and camps. One strange factor in the epidemiology of this disease is the fact that, as a rule, this disease does not spread rapidly and in the broadcast manner that scarlet fever and measles do. We commonly have an invasion in a school or locality, a certain number of cases occur, the disease dies down and that is the end of it. More rarely, however, mumps does extend broadcast and invade the whole of a district. Epidemics of this sort were described by the famous French physician, Laveran. Similar epidemics in Italy, Switzerland and Sweden have been reported.

The disease under consideration has been known by many names. The Latins called it ''cynanche parotida''; among the French it is called ''les oreillous''; ''the branks'' was an old Scottish term for the mumps. The word ''mumps'' comes to us, perhaps, from the Danish term, ''Mompen,'' meaning mumbling (like an old man), to talk in an imperfect fashion. The swelling about the throat and the inability to open the jaws causes the patient to talk in an imperfect or mumbling tone, hence the popular term or its corruption, namely, *mumps.* The proper scientific term for this disease is *parotitis epidemica.*

CHAPTER XVI

SYPHILIS

By Victor D. Lespinasse, M.D., F.A.C.S.

Acquired syphilis, p. 329—Etiology, p. 329—Bacteriology of Treponema pallidum, p. 329—Morphology, p. 329—Types, p. 330—Stains, p. 330—Distribution, p. 330—Modes of infection, p. 331—Symptomatology, p. 332—Primary stage, p. 332: The chancre, p. 333—Secondary stage, p. 336: Specific symptoms of the secondary stage, p. 337—Common types of lesions in secondary stage, p. 339—Tertiary stage, p. 344: Syphilids of the tertiary stage, p. 344—Special symptomatology of the secondary and tertiary stages, p. 345—Laboratory findings, p. 355: Blood tests, p. 355—Wassermann reaction, p. 355—Provocative Wassermann test, p. 358—Hecht-Weinberg-Gradwohl test, p. 360—Parasites, p. 361—Tissue, p. 362—Histopathology, p. 362—Cerebrospinal fluid, p. 363—Nonne-Apelt reaction, p. 363—Colloidal gold test, p. 364—Luetin test, p. 364—Special examinations, p. 365—X-ray examinations, p. 365—Ophthalmoscope, p. 367—Cystoscope, p. 367—Laryngoscope, p. 368—Proctoscope, p. 368—Diagnosis, p. 368—Diagnosis in primary stage, p. 368—Diagnosis in secondary stage, p. 370—Diagnosis in tertiary stage, p. 372—Diagnosis in latent syphilis, p. 374—Differential diagnosis, p. 375: Clinical varieties, p. 380—Treatment, p. 381—Prophylaxis, p. 381—General management, p. 382—Local treatment, p. 385—Hydrotherapy, p. 385—Constitutional treatment, p. 386—Mercury, p. 386—Arsenic, p. 401—Plan of the treatment of syphilis, p. 409—Treatment of primary stage, p. 409—Treatment of secondary stage, p. 410—Subsequent treatment, p. 413—Treatment of syphilis during pregnancy, p. 413—Prognosis, p. 416—Pathology, p. 417.
Hereditary syphilis, p. 429—Transmission, p. 429—Factors which determine the development of hereditary syphilis, p. 430—Characteristic symptoms of hereditary syphilis, p. 430—Diagnosis of early hereditary syphilis, p. 437—Diagnosis of late hereditary syphilis, p. 438—Treatment of hereditary syphilis, p. 438.
Distribution and historical summary, p. 441.
Sociological aspects of the disease, p. 444.

ACQUIRED SYPHILIS

Etiology

Bacteriology of Treponema Pallidum (Spirochæta Pallida)

Morphology.—The *Treponema pallidum* is a closely coiled, flexous organism which is long, thin and delicate. It measures from .25 to .04 micron in diameter; the length of the organism varies considerably—from 3 to 15 microns. It consists of from 6 to 12 spirals which are regular in outline. The number of spirals varies with the length of the organisms; there may be only a few spirals or as many as twenty. The ends of the *Treponema pallidum* are attenuated and each end bears a polar flagella; the ends terminate on the periphery of the spiral instead of at the center, as do those of the *Spirochæta bucallis* and some of the other forms. The organism is actively motile and possesses a twofold motion. Besides exhibiting true progressive motion, it also rotates about its long axis, resulting in a corkscrew motion. Undulatory contractions of the organism have been noticed. According to Schaudinn and Noguchi, reproduction takes place typically by longitudinal fission.

Types.—Noguchi has described three types of *Treponema pallidum.* He observed that certain strains of the *Treponema pallidum* differed in appearance and produced different lesions in the rabbit's testicle. He classified the organisms, according to their morphology, into (1) an average or normal type, (2) a type which was thicker than normal, and (3) a type which was thinner than normal. He concluded that the morphological and pathogenic variability in cultures of *Treponema pallidum* might constitute racial differences in the same species.

Noguchi suggested the possibility of the existence of various strains of the organisms which had a predilection for certain tissues, such as the neurotrophic strain. Clinically, there is evidence to support this belief, since persons who are afflicted with marked cutaneous lesions rarely have much nervous involvement, and similarly with the cases of osseous syphilis.

Stains.—The organism does not stain with the usual anilin dyes, nor does it stain by Gram's method. By Giemsa's method, it stains a pink color, while by Levaditi's method the organism stains black or dark brown.

Distribution.—IN THE BODY.—The organism is present in the hard chancre, and in practically all cases its presence can be demonstrated. *Treponema pallidum* is also found in secondary lesions, especially in mucous patches, condylomata and the various skin papules. It is also present in the regional lymph glands. Levaditi was able to demonstrate the organism in the blister fluid of an eight-day-old child afflicted with hereditary syphilis. In the tertiary stage, the organism is present in the lesion, but in such small numbers that it is quite difficult to demonstrate them. The organism is present in the blood during the florid stages of the disease, but *Treponema pallidum* develops much better in the lymphatic spaces than in the blood. It may enter the blood and lymphatic stream directly during infection and locate among the interepithelial lymph spaces and later reach the perivascular lymph spaces.

In case of congenital syphilis, the liver and spleen contain large numbers of *Treponema pallidum.* They are also found in the other internal organs, but not so abundantly. The abdominal viscera are frequently involved in the acquired type of syphilis. The infection is not limited to any special tissues in the body, but it becomes generalized very early and any tissue may be invaded. Noguchi was able to demonstrate *Treponema pallidum* in the brain substance in general paresis; and other investigators have demonstrated that vascular involvement may be very extensive and show the presence of the organism in the vessel walls.

OUTSIDE OF THE BODY.—Under ordinary conditions *Treponema pallidum* is able to survive only a short time outside of the body. It may exist in moist towels, on eating or drinking utensils or on any object with which the syphilitic comes in close contact; but it remains capable of infecting another person within only a few hours after leaving the body of the infected person. The organism simply vegetates and does not multiply.

The organism rapidly becomes sluggish when it is removed from the body tissues, and only rarely is it possible to detect motion in any of the specimens which have been kept at room temperature for 24 hours. However, sections of chancre, or rabbit's testes, may still be infective for 24 to 72 hours, when kept at room temperature or in a refrigerator. Noguchi showed that material obtained at postmortem may occasionally infect a susceptible animal if inoculation is made within 24 hours. The organism is destroyed by heating from 50° to 55° C. for 20 minutes. In properly prepared cultures, the organism may be made to multiply and can thus be carried through many generations. It grows best on a culture medium consisting of an alkalinized agar, which is melted and quickly cooled to from 45° to 50° C., to which sterile ascitic fluid or hydrocele fluid is added, in the proportion of two parts of agar to one part of fluid. Small pieces of sterile testes or kidney from the rabbit must be added to each test tube. *Treponema pallidum* must be grown under anaërobic conditions. The culture is incubated at 37° C. for two or three weeks.

Modes of Infection.—CONTACT INFECTION.—The most common method of contracting syphilis is by direct contact with the syphilitic sore, or with some substance which has recently been contaminated with the secretion of a syphilitic lesion—such as pipes, glasses, knives, etc. The great majority of cases are contracted through the sexual act; a break in the skin is necessary for the infection to take place, but a break which is so small as to be microscopic in size is sufficient for the *Treponema pallidum* to enter the body. Once the organism makes its entrance, it locates in a tissue suitable for multiplication and the infection rapidly becomes generalized. The lesions of all three stages are infective, but the chancre and secondary lesions—such as the mucous patch, papules and condylomata—are most infective, since they contain a large number of *Treponema pallidum*. The tertiary lesions are also infective, since the presence of the organisms in them has been demonstrated.

HEREDITARY TRANSMISSION.—Until recently it was quite generally believed that it was possible for the father to infect the ovum without infecting the mother. This was later shown to be practically impossible, since there was no way of explaining how a sufficient number of organisms could enter the ovum and produce infection. Moreover, an infected ovum would not be very likely to develop, for it has been shown by research on the cells of lower animals, that if a single blastomere was infected the cell failed to develop. Colles stated that a syphilitic child could not infect its mother because the mother was immune; it has been recently shown by means of the Wassermann reaction that the mother was immune because she herself was syphilitic, even though she appeared to be clinically free from the disease. To-day, opinions are quite generally agreed that the transmission of hereditary syphilis is purely maternal.

Cutaneous Inoculation.—Syphilitic virus is occasionally inoculated into the cutaneous tissue. The physician especially may inoculate himself while making a vaginal, rectal or digital throat examination of a syphilitic patient. In case he has a slight cutaneous break and this area comes in contact with some of the material containing *Treponemata pallida* he will be infected. Syphilitic virus may also be inoculated in a healthy individual by means of an infected razor, by tattooing, vaccination and catheters.

Mucous Membranes.—Extragenital chancres are not uncommon. They are, for the most part, purely accidental and innocently acquired. Infection may be acquired during the act of kissing, but it may be acquired from drinking cups or glasses which have recently been used by a person having lesions on his lips or tongue. A case is reported where a young woman kissed her lover, not knowing that he was syphilitic; she later kissed a number of her schoolmates, with the result that six of them became infected. In the rural communities of Russia, syphilis is frequently acquired innocently. The infant becomes infected soon after birth by a kiss from an individual who is syphilitic.

An interesting experience of my own is in a family in which the mother had a tertiary lesion; the baby, two years old, had a papular rash on the body and a healing chancre on the lip; while the grandmother had a typical chancre on the lip.

Infection through Discharges from Mouth and Nose.—Since the lesions which are present in the mouth during the secondary stage of syphilis contain many *Treponemata pallida,* they are naturally very infective. Physicians may become infected from the sputum while making a throat examination of a syphilitic patient. Fournier reported five cases of chancre of the eye where the physician was thus infected, the patient being seized with a spell of coughing and expelling infectious material into the doctor's eye. Discharge from the nose during sneezing may also spread the infection.

Infection through Insects.—There is a possibility that *Treponema pallidum* may be carried from one person to another by means of insects. Thus far, no case of such infection is reported, but the possibility of the bedbug carrying the infection must nevertheless be admitted.

Symptomatology

A. Primary Stage

Period of Incubation.—The chancre, which is the characteristic lesion of the primary stage of syphilis, does not make its appearance immediately after infection, but is preceded by a definite incubation period. This period is variable, but in a typical case occupies from 15 to 30 days, with an average of about 20 days. Occasionally, the chancre makes its appearance in less time than this, but rarely does it occur in less than ten days. Moreover, it may make its appearance as late as forty days following the infection. The period of incubation varies with the virulence of the organism and the receptiveness of the patient.

The Chancre.—The incubation period in the primary stage is not characterized by any special symptomatology. The patient, as a rule, enjoys his general good health and the appearance of the chancre is the first symptom of which he is usually aware. The chancre develops in healthy skin and may appear as a round papule, somewhat prominent, of neoplastic consistency, and presenting a slightly radiating center. The lesion is painless and not sensitive to pressure, unless secondarily infected. In the early stage of its development, the chancre is seldom observed, but as time goes on the lesion becomes larger, more prominent, indurated, and may ulcerate. For the most part, the chancre syphilitica is single, but multiple chancres may occur. It is rare for more than three or four chancres to be present on the same person. Multiple chancres usually occur in about one case in ten, although some authors report a slightly higher percentage. The chancre may be one of various types.

TYPES OF CHANCRE.—(*a*) *Eroded Type.*—The eroded type of chancre is a small, smooth, circular, superficial lesion, characterized by a very slight, thin induration. The induration may be practically absent or may be so slight as to produce a parchment-like feeling when the lesion is palpated. The chancre is usually of a dark red color, resembling the appearance of fresh meat, but it may be somewhat grayish in appearance. The lesion may exist as an elevation, a depression in the surrounding skin, or simply as a circular, eroded induration without either elevation or depression. In this stage there is a slight seropurulent discharge from the chancre.

(*b*) *Indurated Papule.*—This type of chancre is not very common. It is usually located on areas of skin which are dense and thick, with the result that the lesion does not present the extensive induration characteristic of the common types of syphilitic initial lesion. The indurated papule consists of a small, flat papule, which is dark red in color, the base somewhat indurated and the apex surmounted by a small scale.

(*c*) *Hunterian Chancre.*—This type of chancre is common and is the lesion usually pictured when the expression "hard chancre" is used. The chancre shows a distinct ulceration, which may be quite extensive; its base is markedly indurated. The ulcer invades the epidermis and presents a funnel-shaped appearance, due to its smooth, sloping edges. Granulation tissue is present at the base and a membrane is sometimes adherent over the lesion. The ulcer may discharge a sanguineous exudate.

(*d*) *Other Types of Initial Lesion.*—Various other types of initial lesion are occasionally seen, such as:

I. *Silvery Spot:* This type occasionally occurs on the glans penis and resembles the spot produced when the skin is touched with the nitrate of silver cautery stick.

II. *Herpetiform Type of Initial Lesion:* This type of chancre consists of a superficial ulceration, with an exudation of characteristic herpetic vesicles. Both of these types of chancre are very rare, but the induration may nevertheless be very marked.

III. *Diffuse Syphilitic Edema:* This lesion is characterized by a diffuse, extensive, brawny, non-painful edema. It occurs chiefly on long prepuces and on the vulva.

(*e*) *The Mixed Chancre.*—The syphilitic infection may coexist with the chancroidal ulcer and be completely masked. The nature of the lesion depends upon the virus which was first inoculated. In case of simultaneous inoculation of both viruses, the lesion presents the appearance of a chancroid, since the incubation period of the chancre is much longer than that of the chancroid and the chancroid is a destructive lesion, destroying the infiltration faster than the luetic infection can build it up.

DURATION OF PRIMARY LESION.—The ordinary ulcerated chancre lasts five weeks on an average. The erosive type of chancre disappears more rapidly, whereas the indurated chancre lasts a much longer time. Treatment, and especially treatment with arsenobenzol, hastens the healing of the chancre.

VARIOUS FORMS OF CHANCRE.—Although the majority of chancres occur on or about the genitals, chancres occasionally occur on other parts of the body. Extragenital chancres frequently occur on the lips, tongue, tonsils, mucous surfaces of the mouth, pharynx, fingers, face and mammary glands; but any part of the body may be affected.

(*a*) *Chancre of the Lip.*—This type of chancre may occur on either lip, but the lower lip is the more frequently involved. The lesion is usually located in the median line, or slightly to one side, and at the junction of the cutaneous and mucous surfaces. Usually it begins as a simple chap, fissure or erosion, and presents no effect which is especially characteristic, until a few days later, when it becomes indurated. Later, the characteristic lymphatic enlargement also occurs in the regional lymph glands.

(*b*) *Chancre of the Tonsil*—This type of primary lesion is rare and difficult to diagnose. The chancre appears inflamed and when palpated with the finger, induration is observed. It may be erosive or ulcerative in type. Lymphatic glands begin to enlarge about two weeks following its appearance.

(*c*) *Chancre of the Tongue.*—Not uncommonly the tongue is the seat of a syphilitic chancre. The chancre is usually located on the anterior portion of the tongue, but may be on the sides or dorsum. The chancre is usually erosive in type and similar to the genital chancre, although the ulcerative type of lesion is also seen. The ulceration usually becomes deep and extensive, and induration very marked.

(*d*) *Chancre of the Finger.*—Chancre of the finger is most commonly seen at the edge or base of the nail. Its development is insidious and the chancre may scarcely be observed. It may begin as a simple erosion and may be papular in type. Physicians and nurses are most frequently affected by this type of chancre. It is painless, secretes very slowly, and is indurated.

(*e*) *Chancre of the Eyelid.*—Not infrequently, the eyelid is the seat of a syphilitic chancre, caused by its infection with sputum. Children may become infected by their eyes being anointed with the saliva of a syphilitic and, occasionally, by using the common towel. Physicians are sometimes infected with the sputum from a syphilitic patient during the act of coughing, while the physician is examining the patient's throat. The chancre may occur on the conjuctivæ or it may be located on the lid.

(*f*) *Chancre of the Breast.*—The nipple is the most frequent seat of chancre of the breast, but chancre may also occur on the skin covering the gland. It may appear as a simple fissure, crack or erosion. As the lesion develops, it gradually becomes indurated, a slight discharge is observed, and it is soon followed by lymphatic enlargement.

Lymphatic Enlargement.—The syphilitic virus rapidly attacks the lymphatic vessels and ganglia. Enlargement of the lymphatics is frequently noticed a very few hours after the appearance of the chancre. When the chancre is located on the prepuce or on the glans penis, lymphatic vessels on the dorsum of the penis are especially liable to be involved. Such involvement manifests itself as an indurated cord, along the center of the dorsum of the penis, which resemble a necklace; or it may be smooth.

The regional lymphatic ganglia are first and always most extensively involved, but the adenopathy rapidly involves the lymphatic glands of the entire body. The glands become hard and enlarged, but are not painful to pressure or motion. As the result of irritation or secondary infection of the chancre, the glands become still larger in size and become painful to pressure and motion. Some degree of periadenitis may occur, mating them together in a single irregular, large, painful, adherent mass. Suppuration rarely occurs. The lymphatic enlargement following the appearance of a syphilitic chancre is not necessarily limited to the region in the most direct relation to the sore. Both sides are usually involved, but, occasionally, only the glands on the side opposite the chancre are affected. The glandular involvement does not disappear for several weeks following the appearance of the chancre, and it may even last several months.

Blood Changes.—Alteration in the blood picture is observed during the primary stage of syphilis. As a rule, this change consists of a severe anemia of the chlorosis type.

B. Secondary Stage

Period of Incubation.—The secondary period of incubation occupies the time from the appearance of the initial lesion to the time of cutaneous eruption. The usual duration of this period is 42 to 45 days, or approximately six weeks following the appearance of the chancre. This period of incubation is very variable and depends upon the virulence of the organism and the receptiveness of the patient. *Treponemata pallida* are generally distributed throughout the body during the secondary incubation.

General Constitutional Symptoms.—The secondary stage of syphilis is characterized by general constitutional symptoms, such as loss of weight, and strength, mental depression, anorexia, headache, angina syphilitica, enlarged spleen, blood changes, lymphatic enlargement, bone pains and fever. The patient has a general feeling of fatigue, which resembles the fatigue one experiences during an attack of the grip. He complains of various pains and aches. Headache is one of the most characteristic symptoms during this stage of the disease. The headache consists of a dull ache which usually becomes worse at night; he may complain of violent shooting pains in the temporal regions and of a dull ache in the back of the neck and in the occipital region. Fever may be well marked, but as a rule it is only slight and, therefore, generally overlooked. The temperature may, however, rise to 103° F. and simulate typhoid fever. It reaches its maximum in the evening and gradually decreases toward morning. Fever is similar to that of the acute exanthemata, in that it disappears gradually after the cutaneous eruption occurs. The patient may lose weight rapidly, but in the great majority of cases the loss is slow and ranges from one-half to two pounds weekly. When the loss of weight is gradual, it may not be detected, unless the patient is regularly weighed, until a considerable period has elapsed and the loss becomes very noticeable. The patient may lose as much as ten to thirty pounds in the course of six months following the infection. This loss of weight is gradually regained during proper treatment.

Blood Changes.—Anemia is observed during this stage of syphilis. It is variable in type, and the degree of anemia depends upon the severity of the lesion. Many patients who suffer little with the disease show very slight blood changes. As a rule, the blood picture is that of a chlorotic anemia, but it may simulate other types of anemia and occasionally it presents a picture which resembles an atypical pernicious anemia. With the appearance of the rash, there is a fall in the number of red cells and a decrease in the hemoglobin. The red cells may be decreased to 3,000,000, while the hemoglobin may be decreased to 60 or 70 per cent. Administration of mercury in proper doses causes an increase in the red cells, but prolonged excessive doses cause a reduction in the number of red cells.

Lymphatic Enlargement.—Lymphatic glands are involved early and extensively by the *Treponema pallidum*, causing a characteristic enlargement. This is one of the earliest signs of secondary syphilis. The adenopathy is generally distributed throughout the body, but it is best observed in the epitrochlear, suboccipital, cervical and axillary glands. The adenopathy which occurs at this time is pathognomonic of syphilis. The degree of adenopathy does not necessarily determine the degree of severity of the syphilitic infection.

SPECIFIC SYMPTOMS OF THE SECONDARY STAGE

Changes in the Hair and Nails.—(*a*) Alopecia Syphilitica.—Syphilitic alopecia is of frequent occurrence during the secondary stage. It is most common in those cases which have received insufficient treatment or no treatment at all. It occurs without being preceded by a scalp disease, or without any noticeable exfoliation or itching. The falling of the hair gradually becomes more abundant until, after a few days, small zones of alopecia are observed. These zones are quite extensive, multiple, and are scattered all over the scalp; the alopecia is not complete, thus giving the hair a moth-eaten appearance. The eyebrows are occasionally attacked at the time the eruption makes its appearance on the chest. This type of alopecia is almost pathognomonic of syphilis, but it is occasionally seen in other conditions, such as tuberculous lesions and during the convalescent period of grave diseases. In the latter conditions, however, the areas of alopecia are larger than those of syphilis. Syphilitic alopecia usually begins during the first three months of the disease, and it does not cause permanent baldness. Pedersen believes that syphilitic meningitis occurs, associated with syphilitic alopecia, more than with any other clinical manifestation. He bases his conclusion on the investigations of Cyranks and Gartner, who found the cerebral spinal fluid to be pathological in 33 out of 35 cases of alopecia and in 10 cases of his own of alopecia, the spinal fluid was positive in 8 cases and negative in 2 cases; these two had been given extra energetic treatment.

(*b*) Syphilitic Onychia and Perionychia.—Secondary syphilis of the nails is not uncommon, the finger nails being more frequently affected than the toe nails. For the most part, the affections are multiple and bilateral.

(1) *Forms of Syphilitic Onychia.*—Various types of syphilitic onychia are observed. Atrophic onychia is rather common in early syphilis. Infection of the nail may be very slight, in which case it is thin, ragged and brittle. If the infection is of a more severe nature, the nail becomes thickened at its corners, presents pearly edges and is very easily broken from the nail base. Severe atrophic onychia is usually associated with perionychia. Partial separation of the nail is not an uncommon condition and when it occurs, it is usually associated with palmar syphilids. Because of the presence of syphilids, the nail becomes raised gradually from its base along the whole extent of its edge. Still more uncommon is complete detachment of the nail. This condition occurs only when the matrix itself is involved. Hypertrophic onychia, which con-

sists of an unusual thickening of the nail, is an extremely rare condition.

(2) *Forms of Perionychia.*—Perionychia may occur as a dry form, in which condition the ridge of the nail is surrounded by syphilids simulating palmar squamous syphilids. The skin may be greatly hypertrophied and cracked. In inflammatory perionychia, the bed of the nail is inflamed, thickened and very painful. Syphilitic inflammatory perionychia may be confused with other types of inflammatory perionychia, but the fact that it runs a chronic course usually serves to differentiate it. There is little tendency for syphilitic perionychia to suppurate. Rarely, ulcerating perionychia is observed, which consists of an ulceration about the base of the nail with an abundant proliferation of granular tissue.

Ocular Syphilis.—Syphilitic iritis is the most common form of ocular involvement. It is most commonly observed during the secondary stage, making its appearance soon after the first cutaneous eruption. Syphilitic iritis usually makes its appearance within the first year following the infection. It occurs either as a simple plastic iritis or as a parenchymatous type. Plastic iritis often occurs about the second month of the disease; it is characterized by intense supra-orbital pain—which is most intense during the night, and by sluggish, contracted pupils. The iris is discolored and fixed to the lens. Circumcorneal, deep injection is marked. In the parenchymatous type, yellowish-red nodules which are of the size of a pin-head or larger are observed on the inflamed iris, both at the pupillary and ciliary border. Such nodules are very characteristic of syphilis.

Aural Symptoms.—The ear may become involved during the secondary stage of syphilis. Such involvement may manifest itself by tinnitus, deafness and vertigo. The onset of these symptoms may be very insidious. The deafness produced by syphilitic acoustic neuritis may be slight, and the patient thus be able to hear a voice very well. He is able to hear tuning forks of the low pitch well by air conduction, but may hear the high pitched forks poorly. The patient may complain of vertigo, nausea or vomiting, and spontaneous nystagmus may be observed. Of the latter symptoms, vertigo is by far the most common.

Nervous Symptoms.—Nervous disturbances are fairly common and are of grave importance. Acute arterial disease may lead to thrombosis of the cerebral arteries and result in softening. Rupture of the artery usually occurs in the tertiary stage of syphilis. Acute meningeal myelitis and peripheral neuritis, with paralysis, are rather common. The tendon reflexes are at first increased, but later they become depressed and may even disappear altogether.

Syphilitic Arthritis.—Syphilitic arthritis is an early symptom of secondary syphilis. Dull pains occur in the joints and extremities, which resemble rheumatic pains. A slight effusion may be present, but as a rule the joints are not red, swollen or tender. Pains are most intense at night. Later in the course of the disease they become sharp and intermittent in character. Osteoscopic pains occur at various points, such as the inner third of the ribs. Distinct tenderness may be observed at these points. The muscles and joints frequently feel stiff.

Angina Syphilitica.—Sore throat is a common symptom of the secondary syphilitic infection. The tonsils become swollen and the throat is sore. The soft palate and uvula are frequently affected. The throat appears inflamed and is of a dark red color. Tumefaction of the inflamed tissue from healthy tissue is very marked and constitutes a sign which is of considerable diagnostic value.

Skin Eruption.—The occurrence of a skin eruption next takes place. The types of lesions produced are extremely numerous, and they may simulate almost any type of skin disease. However, there are certain characteristics of the syphilitic lesions which more or less serve to identify their syphilitic nature.

(*a*) *Form.*—The syphilids are a round, sharply defined cellular infiltration of the papillary and superficial parts of the corium. They have a tendency to heal without producing any scar tissue.

(*b*) *Grouping.*—The eruption has a tendency to become generalized, bilateral and asymmetrical; and they have a predilection for certain areas of the body. The sites most frequently affected are the face, the forehead, the areas about the nostrils and mouth, the soles of the feet, the palms of the hands, the region about the anus and the genitals. The lesions may be abundant or somewhat scanty. The syphilids have a tendency to occur in groups and arrange themselves in circles or semicircles or become annular. This tendency is most marked in the later lesions.

(*c*) *Color.*—The early lesions are a bright red in color, due to cutaneous congestion and local inflammation. This color rapidly changes to a dull red, which may acquire the color of raw ham or the lesions may be of a copper color. A certain amount of pigmentation is present, but this is not prominent. The color—copper or raw ham—is very characteristic of syphilids, but this finding must be taken in conjunction with other diagnostic points in making a diagnosis of syphilis.

(*d*) *Polymorphism.*—The syphilitic lesions are multiple or polymorphic in type. Macules, papules and pustules, along with the scaly patch, may be indiscriminately intermingled. Polymorphism is especially noticed during the early course of the disease. As the disease grows older, the lesions become more uniform in type.

(*e*) *Subjective Symptoms.*—As a rule, subjective symptoms do not accompany the syphilitic eruption. The patient does not complain of pain or itching, except in rare cases. The negro occasionally complains of a slight itching, but this is not intense enough to cause him to scratch. The miliary papular and miliary pustular lesions are the lesions which are most likely to cause itching. Only rarely do these lesions cause itching in the white race.

Common Types of Lesions in Secondary Stage.—The most common types of lesions in the secondary stage are erythematous or macular syphilid, papular syphilid, vesicular syphilid—which is relatively rare, and the pustular syphilid. With the exception of the erythematous syphilid, these are all subdivided into other varieties, depending upon the size and shape of the lesions.

(1) ERYTHEMATOUS SYPHILID (*Roseola, Macular Syphilid*).—The erythematous syphilid is the most common form of secondary syphilid and is the first to make its appearance, developing six to eight weeks after the chancre. The lesions appear at almost the same time that the lymphatic enlargement is noticed. The eruption consists of spots which vary greatly in size from that of a small pinhead to the size of a dime, or larger. The lesions are generally round or oval, but they are occasionally irregular. They first appear as rose-colored, but gradually change to a yellow as they begin to disappear. The lesions are not raised nor squamous, and are generalized. They may appear on any part of the body, with the exception of the face; however, a few isolated syphilids may be noticed on the forehead. The lesions have a predilection for certain parts of the body, such as the sides of the chest, the groins and the flexor surface of the forearms. The number of spots increases during the first week, and these remain for some time. Occasionally, the lesions present an annular appearance. This type of lesion makes its appearance later than the ordinary macular syphilid. These types of erythematous syphilid show a tendency to recurrence in the tertiary or late secondary stage.

(2) THE PAPULAR SYPHILID.—This type of syphilitic skin lesion is very common. Various varieties of the papular syphilid are observed, depending chiefly upon the size and shape of the lesion and their location. The lesions may be flat or acuminate and they may be large or small. The lesions appear as hard elevations and present the characteristic copper or raw ham color.

(3) THE SMALL, FLAT, PAPULAR SYPHILID.—This type of eruption appears as a small, red and brownish-red lesion, which varies from 3 to 6 millimeters in diameter. The lesions present a smooth appearance early, but most of them become somewhat scaly and are surrounded by a sort of collar. The papules are usually very numerous and well scattered. The forehead is frequently affected, and especially at the margin of the hair. On the face, the areas about the nose and mouth are involved, while both the anterior and posterior aspect of the trunk are affected. The flexor surface of the arms, the palms and soles of the feet and the region about the clavicles are generally quite free from the eruption. The papular syphilid may become arranged in semicircles or they may assume an annular arrangement. For the most part they are discrete, but coalescence does occur with the production of plaques. The annular patches most frequently involve the face and they are especially noticed in the region about the mouth, on the chin, cheeks and forehead. This type of lesion usually makes its appearance within from three to six months after the infection. To begin with, it is usually associated with the macular type of syphilid. The lesion may last for months; when it disappears, slight pigmentation is left at the site of the papule. This pigmentation disappears in time.

(4) Large, Flat, Papular Syphilid.—This type of syphilid first appears as a small red spot, which gradually increases in size and becomes elevated. The papule thus produced varies in size from six to twelve millimeters. It is smooth or but slightly scaly and brownish-red in color when the lesions are completely developed. The forehead, back of the neck, lower portion of the face, upper part of the back and flexor surface of the limbs, along with the inner aspect of the thighs, the palms, soles and the region about the genitals and anus are the sites most commonly affected. As a rule, polymorphism is not very well marked during the occurrence of a large, flat, papular syphilid. The eruption is usually quite uniform.

(5) Condylomata Lata.—When syphilitic papules are located on the areas of skin which are opposed to each other and which are more or less moist—such as the mucous surfaces at the angles of the mouth and about the anus and vulva, beneath the foreskin or on the scrotum—abraded surfaces may appear. These resulting lesions give rise to a secretion, and then they are called moist papules. They are more or less covered with an adherent membrane. The moist papules may become infiltrated and hypertrophied and give rise to cauliflower-like warty growths known as condylomata lata. The surface appears grayish-white and may be excoriated. These condylomata lata are elevated and the surface usually appears raw. Infiltration is usually very marked and it is sometimes difficult to demonstrate the papillary nature of the lesion. Vegetated papules are occasionally observed; they appear as large cauliflower-like, warty growths and are most frequently observed on the face, scalp, shoulders and genitals. They are frequently accompanied by abrasion and crusting of the adjacent skin.

(6) Follicular Syphilid (*Miliary Papular Syphilid or Acuminate Papular Syphilid*).—The follicular syphilid occurs both as a large and as a small form. These two forms very commonly occur together; the lesions are located about the opening of the hair follicles. They are acuminate in shape and vary in size from that of a pinhead to a millet seed or larger. The follicular syphilid first appears bright red in color, but later on this changes to a brownish-red. As a rule, a small scale caps each lesion. The time occupied for the appearance of the eruption varies from two to fourteen days; most frequently, from ten to twelve days is the time required. The face, the scapular region, the upper arm, the thighs and the trunk are the most common sites for the lesion. This type of syphilid occasionally occurs in patches, which may be annular.

(7) Vesicular Syphilid (*Herpetiform Syphilid*).—This type of skin eruption is extremely uncommon; its existence has even been denied. Various varieties have been described, differing according to size and arrangement of the lesions. The vesicles may be small or large; they may be generalized or occur in groups, affecting only certain regions of the body. They are observed on the face, the trunk and the extremities, and have a tendency to appear about the hair follicles. The eruption may simulate that of eczema and appear as a general eruption of small

vesicles, which may be either discrete or occur in patches. As a rule, the face is spared. If the vesicles are discrete, a copper-colored areola usually surrounds each lesion. The vesicular fluid may remain clear, break through the epidermis and give rise to a slight crust. Frequently pustulation occurs and leads to the formation of thin, yellow crusts and temporary pigmentation.

The vesiculoid form of papular syphilid consists of numerous discrete vesicles on the top of a papule. They are about the size of a split pea and may be either globular or umbilicated. These lesions may persist for some time and then rupture, producing the formation of a thin crust and pigmentation. Sometimes they become pustular and crust.

(8) PUSTULAR SYPHILID (*Acneform Syphilid; Pustulocrustaceous Syphilid*).—The pustular form of syphilid is less frequent than the macular and papular types, but it is by no means uncommon. They may occur during any period of the secondary stage or during the tertiary stage. In general, they resemble the papular syphilid in morphology and arrangement of the lesions. The lesions may be pustular from the beginning, or they may begin as papules. They are classified into large, small, flat or acuminate varieties.

(9) THE SMALL ACUMINATE SYPHILID.—This eruption consists of minute, miliary pustules, located about the hair follicles or the mouth of a sebaceous gland. A small, yellow crust is formed, producing pigmentation. The lesion is of the same size as the corresponding papular syphilid, varying from the size of a pinhead to that of a millet seed. It begins as a small, red papule, capped with a pustule or vesicopustule, the contents of which, later, dry and produce small crusts. As these fall off, pigmentation is observed and rarely a small scar. The eruption may appear within two or three days and be very general, or it may occupy a period of ten to fourteen days before it is developed. As a rule, it appears during the first six months of the disease. It rarely ever occurs as an early eruption, but it may be seen quite late. The course is usually sluggish and the lesions usually remain several months.

(10) LARGE, ACUMINATE, PUSTULAR SYPHILID.—Large, acuminate, pustular syphilids may appear as lesions the size of a split pea, and closely resemble ordinary acne. They begin as a macule, which becomes changed into a papule and later into a pustule. The syphilids are usually located about the hair follicles and upon a copper-colored infiltrated base. After one or two weeks, the pustule ruptures and leads to production of crusts. When the crust falls off, small ulcers or copper-colored papules are noticed. There is usually some scar formation, but the pigmentation gradually disappears.

(11) SMALL, FLAT, PUSTULAR SYPHILID (*Syphilitic Impetigo*).—The small, flat, pustular syphilid appears as a pustule about the size of a pea. The lesion is arranged in patches which are not very definite, or it may be without definite arrangement altogether. The contents of the pustule may dry and produce brown crusts; these crusts may be discrete when the lesions are not very numerous. However, if the lesions

are numerous and closely placed, considerable areas may be involved. Such areas as the scalp, the brow and the pubes, which bear hair, are especially affected, but the face may also be involved about the corners of the mouth, the nose and the chin; but the lesions may occur on other parts of the body. As a rule, this type of syphilid does not appear until in the late secondary or early tertiary stages.

(12) LARGE, FLAT, PUSTULAR SYPHILID.—This may occur within the first year following the infection, but as a rule it appears about the seventh month. The lesions are usually superficial, but may invade the deeper layers of the skin. A thick crust caps the lesion. On removal of these crusts, ulcerations or erosions are observed which are superficial. However, most of the papules disappear without leaving any trace, except a slight pigmentation which also gradually disappears. This type of skin eruption may appear within a very short time, but frequently it comes out in crops and occupies several weeks in its development. The scalp, extremities and trunk may be involved. When the ulcerations are infiltrated, deep scars are much more likely to remain. This deep type of pustular syphilid is insidious and may last for a month or even a year. New crops make their appearance from time to time.

(13) PIGMENTARY SYPHILID.—Pigmentary syphilid is dependent upon the local deposit of an excess of pigmentation. The lesion may appear as rounded, oval or irregular, brownish plaques, whose borders are well defined, and which vary in color from a yellowish-brown to a deep brown in color. This type of lesion varies in size from three to two and one-half millimeters in diameter. A diffuse pigmented syphilid may occur, which appears as a small, flat, non-infiltrated macule and then gradually increases in size. The syphilids may vary in their degree of pigmentation, some of the lesions appearing darker than others, while some will have leukodermic spots of varying size in the center of each lesion. The neck is the most frequent site, but the trunk may also be involved. This eruption usually occurs early in the secondary stage, but it may appear much later. After two or three months it usually disappears, but it may last for months or even several years.

(14) MOIST PAPULES.—When the papular syphilid is situated on areas which are opposed to each other and therefore more or less moist, they become of a yellowish-white, or grayish-whitish color and secrete a sort of purulent discharge. This type of lesion is known as the mucous patch. It may become elevated, have a warty appearance and form the condyloma. Mucous membranes, such as the lips, cheeks, palate, tongue, labia and anus, are most commonly affected. The papule appears round, oval and irregular; it is flat and only slightly elevated. The lesions may become eroded or slightly ulcerated. The mucous patch is most frequently seen in the oral cavity or on the lips, while the moist papule is most generally seen about the scrotum, perineum, vulva and anus.

C. Tertiary Stage

Period of Incubation.—There is no definite period of incubation for the tertiary stage of syphilis, such as there is for the secondary stage. It may begin a few months after the cessation of secondary symptoms or it may appear as late as fifty or fifty-five years following the initial infection. However, the average period is from three to five years following the appearance of the chancre. It is during the tertiary stage of syphilis that the visceral changes are most frequently observed; but they are not confined to this period, as any part of the viscera may be affected during the secondary stage of the disease. Since any portion of the viscera is subject to involvement, the organs of each system will be considered separately.

Syphilids of the Tertiary Stage.—The syphilids of the tertiary stage of syphilis have certain characteristics which differentiate them from lesions observed during the secondary stage. As a rule, they are less numerous and their distribution is not symmetrical. They run a chronic course and show a tendency toward ulceration. Most common among the tertiary syphilids are the nodular or tubercular syphilid, the gumma, and the papulosquamous syphilid.

(1) NODULAR SYPHILID (*Tubercular Syphilid*).—The nodular syphilid manifests itself by a dull red or brownish-red elevation, about the size of a large pea. These papules are grouped into patches which vary somewhat in size. The surface appears smooth or somewhat branny. The lesions are arranged in circles or semicircles. Occasionally, the nodules ulcerate and the ulcers assume the shape of a crescent; as healing takes place, scarring may occur. Frequently, there is an area of increased pigmentation about the patches. This lesion is seen most frequently in the tertiary stage of syphilis, but occasionally it is also seen in the secondary stage. Usually, only a single patch is present; but this is not necessarily the case, since several patches may occur. The nodular syphilid may occur as late as ten years or more following the initial lesion, or it may appear as early as two or three years following the initial infection. The face is the site most frequently affected, but no portion of the body is exempt.

(2) GUMMATOUS SYPHILID.—This type of syphilitic lesion is characteristic of the tertiary stage of syphilis; occasionally it occurs in the secondary stage. The lesion develops as a firm nodule, located in the subcutaneous tissue. It gradually increases in size and becomes adherent to the skin; it varies in size from the size of a hazelnut to the size of a small egg. The overlying skin becomes dark red to bluish in color and finally ruptures, allowing the discharge of a bloody, gummy fluid. The ulceration becomes quite deep and may extend to the subcutaneous tissue. The gumma may persist for several months or even years. Infiltration may become quite diffuse, and later be followed by ulceration at various points; these coalesce and form extensive ulceration, with a tendency to crescentric outlines. Occasionally, the gumma before ulceration occurs. The legs are the most com-

mon site for the occurrence of these lesions, but they may appear on other parts of the body, such as the sternum, the scalp, thighs and buttocks. Necrosis of the bone may result from gummatous infiltration of the periosteum. Pain is usually absent, unless the gumma is so situated as to produce pressure. The gumma is usually single, but may be multiple.

(3) PAPULOSQUAMOUS SYPHILID.—The papulosquamous syphilid consists of a scaly, papular eruption, which is limited to the palms and soles. It may appear as scaly patches which are somewhat elevated at their edges and are brownish-red in color or yellowish; or it may appear as flat nodular lesions capped with thin scales. The lesions are quite definitely defined and vary in size from several millimeters to about twelve millimeters. The eruptions are asymmetrical and usually affect only the single palm or sole. Sometimes the palm and sometimes the sole may be affected, but only rarely does the eruption occur on both palms and soles. Sometimes the syphilid may appear with a round or oval contour and be of a light red to a red color. This type of syphilid is surrounded by a narrow collar of thickened skin, the edges of which are eroded. This form of eruption may last for months or years, and constitutes one of the most difficult forms of syphilitic skin eruptions which we have to combat. It shows a marked tendency toward recurrence.

SPECIAL SYMPTOMATOLOGY OF SECONDARY AND TERTIARY STAGES

Gastro-intestinal Tract.

ESOPHAGUS.—Gummata or ulcers of the esophagus rarely occur; when present, they produce a deformity of the passage; or perforation may occur, leading to a tracheo-esophageal fistula and a subsequent septic bronchitis. Cicatrization of the gummata leads to progressive stricture which may be readily confused with carcinoma. Local dilatations are often necessary but systemic treatment should not be omitted.

STOMACH.—Organic gastric syphilis is rare except in advanced cases. It occurs usually between the ages of 35 and 40 years; on an average from 10 to 12 years after the initial infection, and the duration is about two years. Syphilis of the stomach manifests itself in various ways. Acute catarrhal gastritis, which occurs during the secondary period, is the result of the toxemia, rather than an organic lesion, which is rare. Chronic gastritis is more common and is usually responsible for the anemia and malnutrition which are present. Ulcers of the stomach, due to syphilis, are relatively rare, and are the result of an endarteritis. White was able to determine syphilis as the etiological factor in ½ per cent. to 1 per cent. of his private cases. He obtained a positive Wassermann in less than 2 per cent. of 204 hospital cases.

Gummata of the stomach are rare. When they occur, they are generally multiple. A gummatous tumor may occur and lead to obstruction. Cicatricial formation may occur and lead to a contraction of the stomach wall. The symptoms of syphilis of the stomach are not particularly unlike those due to non-syphilitic lesions. Pain soon after eating is very constant; rapid emaciation occurs and may be the symptom for which the patient seeks medical advice. A slight temperature may be noticed. Hemorrhage is present in about 30 per cent. of the cases and may be the first symptom; it is sometimes fatal. Vomiting is quite likely to occur and achylia is observed. Free hydrochloric acid, if present, is found to be very slight in amount.

Treatment of syphilitic lesions of the stomach is, as a rule, very satisfactory. This is especially true when the trouble is diagnosed early and the pathological progress is not too far advanced. The diagnosis depends upon the history of the patient. Careful observation is necessary, over a period of time, to eliminate other common diseases of the stomach. After these conditions are eliminated the therapeutic test will help to establish the diagnosis of syphilis. The final diagnosis depends upon the Wassermann test and the *x*-ray.

INTESTINES.—Ulcerations and gummata occasionally occur in the intestines, and may give rise to grave symptoms of hemorrhage or obstruction. Chronic diarrhea sometimes results which may become bloody, and lasts for a long time. It does not readily respond to treatment and leads to a cachexia which very closely resembles the cachexia of carcinoma. Repeated hemorrhages may also result. Constrictions, dilatations or perforation may follow severe ulceration. The appendix is predisposed to a latent involvement. Gaucher states that a large percentage of appendicitis early in life is syphilitic in origin. In 33 cases of appendicitis in infants he found the Wassermann test positive in 11 instances (43 per cent.). Enterocolitis in hereditary syphilis is very grave.

RECTUM.—The rectum is the most commonly involved portion of the gastro-intestinal tract. This is especially true in females, probably indirectly caused by constipation. Gummata and ulcerations are not uncommon and result in stricture of the rectum. The stricture is usually located within the lower 3 or 5 centimeters of the rectum and is accessible to touch. Fistula may also occur.

Treatment should include local measures, as progressive dilatation, as well as systemic treatment. The early lesions of syphilis involve the rectal mucosa but usually pass entirely unnoticed or are given little attention. The symptoms are often very vague, and diagnosis without visual inspection is difficult. Patients with luetic ulcers in the rectum usually show a positive Wassermann test which establishes the diagnosis quite definitely.

SALIVARY GLANDS.—Salivary gland infection, due to syphilis, is quite rare. Gerber, however, has been able to collect 37 cases from the literature. In 28 cases, there was an involvement of the parotid; of the remainder, the sublingual and submaxillary glands shared about equally. The swelling simulates a parotid tumor in appearance, or a chronically infected gland. There is a progressive swelling, which is not tender. If the gland is involved early in the disease, the onset is sudden and the swelling disappears quite rapidly; if it comes at a late stage in the disease there may be no other manifestations of syphilis, and the swollen gland may be mistaken for a neoplasm. However, the syphilitic swelling will be reduced to normal in four to six weeks by appropriate antisyphilitic treatment.

LIVER.—The involvement of the liver in syphilis is frequent. It occurs in about 5 per cent. of cases of tertiary syphilis and is usually due, in that case, to gummata of some size or to a general biliary cirrhosis. Clinical manifestations, however, occur even in the secondary stage and exhibit themselves in the form of:

(1) *Syphilitic Jaundice.*—This is caused by a syphilotoxic parenchymatous hepatitis and not by an obstructive jaundice. The symptomatology is jaundice, temperature, slight enlargement of the liver, more or less liver tenderness and mild to moderate constitutional disturbances. These symptoms all rapidly disappear under proper treatment.

(2) *Acute Yellow Atrophy.*—Acute yellow atrophy occurs, for the most part, later in the course of the infection; however, Osler states that 10 per cent. of all cases of acute yellow atrophy occur during the secondary stage of syphilis. The liver is enlarged early in the disease but after a variable period it reduces rapidly in size; the symptoms—vomiting, jaundice, cerebral symptoms, delirium and involuntaries—are severe, and the case progresses rapidly to a fatal termination. Specific treatment is of no value. The clinical course is usually run in one week after the severe symptoms develop.

(3) *Hepatic Gummata.*—Hepatic gummata—simulating tumor—may also occur. It consists of a gummatous mass or a mass of cicatricial tissue which has replaced the gumma. Special symptoms develop when the tumor is of sufficient size and so located as to obstruct the inferior vena cava or any of the large bile ducts. Antisyphilitic treatment usually produces a rather rapid decrease in the size of the tumor mass and alleviates the symptoms. In these cases the iodids are of special value.

SPLEEN.—It was formerly thought that the spleen was only occasionally involved in early syphilitic infection. Recent work, by Wile and Elliott, however, shows that *acute splenic enlargement* occurs in a large number of cases of early syphilis. This enlargement may be present even before secondary manifestations are apparent, and it is probable that it is the earliest syphilitic visceropathy. The enlarged spleen may be tender and may be soft or firm in consistency.

The enlargement usually disappears quite early, after specific treatment is instituted, but the splenic tumor may persist and be the last manifestation of syphilitic infection to disappear.

Perisplenitis is also seen quite frequently, especially where there are other symptoms of a syphilitic infection. It is frequent in congenital syphilis and is then usually associated with a slight peritonitis.

Respiratory Tract.

NOSE.—An initial lesion of the nose is of very rare occurrence. Gummata more commonly develop late. They involve the bone, cartilage, periosteum and mucous membrane of the septum. These gummata show first as thickening of the septum, usually rather diffuse, later they heal down and produce a perforation with ulcerated edges; or they may begin simply as a necrosis with very slight or no thickening, simply a necrosis of a portion of the septum. When the sequestrum separates a perforation is left. Later on the bridge of the nose is depressed, forming the so-called saddle nose.

LARYNX.—Catarrhal laryngitis occurs very frequently (55 per cent.) during the secondary stage. Excesses in alcohol, tobacco and previous laryngeal trouble predispose to the occurrence of laryngeal syphilitic lesions. The larynx becomes red and edematous, the patient coughs considerably, and may become hoarse. A papular laryngitis may occur, analogous to the cutaneous papular rash. Stenosis of the glottis may result, if the ulcers invade the submucous tissue. Gummata of the larynx are usually multiple. If the invasion is extensive, symptoms such as dyspnea, dysphagia, dysphonia and death may occur, due to asphyxiation. Syphilis of the larynx must be differentiated from tuberculosis and carcinoma.

TRACHEA AND BRONCHI.—The trachea in the early period is hyperemic, swollen and even ulcerated. Stenosis may follow the healing of a gumma and produce a deformity in the trachea, causing symptoms such as dyspnea, cyanosis, a frequently recurring cough, with expectoration of a sputum which is purulent or seropurulent. An acute bronchitis may occur during the secondary stage; later a chronic bronchitis occurs. The bronchi may become invaded by gummata, or ulcers may develop. The healing gummata or ulcers may produce a stenosis, or a perforation may result from the erosion produced by the ulcer. Perforation may cause a tracheo-esophageal or broncho-esophageal fistula. In case of perforation, death may result from the hemorrhage or from a septic condition.

LUNG.—Syphilitic pulmonary affections are variable. They are rare and usually occur later in the disease. They do not give rise to any specific symptoms and they simulate the various types of tuberculosis, or occasionally carcinoma or pulmonary hydatids.

Syphilitic phthisis can produce all the symptoms of all the periods of pulmonary tuberculosis: cough, mucopurulent sputum, hemoptysis, dyspnea, intense pleuritic pain, fever and loss of weight may occur. White pneumonia occurs in hereditary syphilis. It consists chiefly of an alveolar infiltration.

MEDIASTINUM.—Syphiloma of the mediastinum and bronchotracheal adenopathy are frequently associated with tracheobronchial syphilis or lung syphilis. They can at times, however, be differentiated. The symptoms are those of mediastinal compression, and there is a particular frequency of obliteration of the superior vena cava or the respiratory tract, and its nerves may be involved. Syphilitic aortitis is frequently coexistent.

Syphilitic pleural disease usually occurs in conjunction with syphilis of the lung. It simulates tuberculous pleurisy very closely, and great care is necessary in making the diagnosis.

Vascular System.

HEART.—It has been shown that invasion of the heart begins at least as early as the first appearance of secondary symptoms or signs, and that serious and extensive lesions occur in the circulatory center. Myocarditis is the most frequent involvement. It begins in the same manner as a fibrous degeneration, fatty degeneration, brown atrophy or any other type of degeneration.

In *acquired syphilis* the front or apex of the left ventricle or the ventricular septum is chiefly involved, while in *congenital syphilis* the right heart is more frequently affected. There is an initial cardiac hypertrophy which is followed by dilatation and even by cardiac aneurysm. Stenosis of the conus or amyloid change may occur. In a series of 50 consecutive autopsies performed by Brooks—some well-treated and some incompletely treated cases—myocarditis was present in 44 instances. Cardiac gummata are not very common, only five cases being discovered in the same series. The gummata may be quite extensive, invade the interventricular septum and lead to heart block.

Coronary involvement is not uncommon. It was found in 35 cases of Brook's series, and five of these were very striking cases in individuals under thirty years of age. Angina pectoris, heart rupture or cerebral embolism may occur. Warthin, after a study of 150 cases of acquired and 50 cases of congenital syphilis, believes syphilis to be the most common cause of cardiac disease.

Pericarditis is almost invariably associated with myocarditis, and it does not present great clinical signs. The signs are usually those of the myocarditis with which it is associated. Syphilitic endocarditis may cause valvular lesions. The aortic valve is most frequently involved. Two-thirds of the cases of pure aortic insufficiency are of syphilitic origin.

Aortitis is a rather frequent sequel. Mussey found that in 1,379 cases of clear-cut syphilis, the heart or aorta was diseased in 4.2 per cent., while Oberndorfer found syphilitic aortitis in 82 per cent. of autopsies of cases with acquired syphilis. In 215 cases reported by Levinson, there was a clinical diagnosis of aortitis in 24 cases (11.1 per cent.). Most cases of aortitis produce trouble between the ages of 40 and 50, but the trouble may occur earlier. Aortitis manifests itself by such symptoms as palpitation, arhythmia, tachycardia, pulse disturbance, precordial pain, dyspnea and substernal dullness. Grossman, in studying 288 cases with secondary syphilis, found arhythmia or pulse disturbance in 85 per cent. of the cases. He found heart murmurs, mostly the result of dilatation, in 40 per cent. Functional disturbances of the heart are quite likely to occur, involvement taking place, from a few months to many years after the initial infection. Aneurysm of the aorta is not infrequent, and Edwards believes that 90 per cent. of aneurysms are of syphilitic origin. They may be single or multiple, and occur, chiefly, in the arch of the aorta. The aneurysms may also be located in the abdominal aorta or its branches.

Veins.—Secondary phlebitis makes its appearance from 2 to 6 weeks after the chancre. It is usually slow and indolent, and discovered only on careful examination. It rarely ever occurs rapidly, and it is seldom painful. Occasionally, it is associated with fever and general symptoms.

The phlebitis is, most frequently, superficial. It may be segmentary in type, extend along the whole length of the vein, or the segments may alternate, diseased segments alternating with the healthy segments. The phlebitis can simultaneously or successively attack many segments of the veins in the patient. The diseased vein produces a reddened area which is slightly edematous, and in the center of which the thrombosed vein is seen. This area is usually free from pain. Very rarely, the phlebitis involves the deep veins. The limb becomes swollen, white and painful on motion. It clears up, in from 4 to 6 weeks, and is never followed by an embolism.

Lymphatic Ganglia.—During the tertiary stage, gummatous adenitis may involve any of the groups of lymphatic glands. Ulcerations may occur which may become phagedenic in type. The blood-vessels are involved by this process, and they may be opened, producing hemorrhage or septicemia, usually with a fatal termination.

Bones and Joints.

Osseous System.—During the secondary stage the patient frequently complains of osteoperiosteal pains. These pains may occur in any of the bones—such as the tibia and cranium—and are usually more severe during the night. Pains may occur in the side, simulating a pleurisy, or in the sternum, simulating angina pectoris. They may be dull or intense, but usually yield quite readily to specific therapy. Late in the secondary or tertiary stage, the periosteal node is palpable. It is the result of a chronic periostitis and is usually found on the tibia. It is at first soft, but later becomes sclerosed. This node is somewhat tender to pressure, and nocturnal aching occurs. It rarely suppurates, and usually improves with general treatment.

The changes and clinical manifestations of the tertiary period are much more pronounced. Gummata occur, which may be either diffuse or circumscribed, single or multiple, and a sequestrum may be present or absent. The gummata produce pains which may be dull or violent, and which are worse at night. These pains are usually quite definitely localized and improve with treatment.

Subperiosteal gummata sometimes lead to the production of caries of the adjacent bone. The vertebræ may be involved, the condition closely simulating Pott's disease. On the other hand, new bone is sometimes developed under the periosteum and leads to osteosclerosis.

Osteitis of the facial bones sometimes leads to perforation which may destroy the superior maxilla, the palate bone or nasal bones. The [illegible] sometimes become perforated. secondary infection enters the sequestrum and meningitis results, which is fatal; or compression of some of the facial nerves, resulting in facial paralysis, neuralgia of the trigeminal or amauroses may occur. Cranial ostitis may produce compression of the brain, which resembles cerebral tumor very closely, in which case it may be necessary to trephine and remove the thickened bone.

Sclerosis may become quite extensive. It may be severe enough to compress and constrict the vessels in the haversian canals and greatly interfere with the vitality of the bone, so that a subsequent pyogenic infection is almost certain to produce necrosis.

Gummata, occasionally, invade the interior of a bone and cause a syphilitic osteomyelitis. The bone expands and secondary thickening occurs, with enlargement of the whole structure. This process may be very resistant to antisyphilitic treatment, in which case it will be necessary to separate the periosteum, freely open the medullary cavity and remove all diseased tissue.

Cases such as these may frequently become confused with malignant growths of the bones; they are quite readily diagnosed, however, by the history of the patient, the occurrence of tertiaries in other parts, rapidity of growth and the Wassermann test.

ARTICULATIONS.—Arthralgia may occur very early and even precede the roseola. It is usually localized in those joints which fatigue rather easily, and the pain is most marked during the night or when the patient lies down. They are relieved by exercise. Subacute synovitis occurs which closely simulates subacute rheumatism; however, it differs from it in several ways which are of clinical value in making differential diagnosis. Syphilitic synovitis affects a small number of joints, usually one or two at a time. The pain is chiefly nocturnal; there is less redness of the skin and less limitation of movement; fever and sweating are less marked than in subacute rheumatism; it reacts to antisyphilitic treatment but not to the salicylates.

Chronic synovitis is manifested by an effusion into a joint. It may be painful or without pain. Although any joint may be involved, the knee is the most frequently affected; the effusion may be extensive enough to produce an hydrarthrosis, which in some cases resists all treatment and leads to disorganization of the joint.

Gummata may invade the perisynovial tissues and manifest themselves as a hard tumor mass producing few symptoms, or they may be diffuse and produce an effusion. In case an effusion occurs, thickening of the capsule or ligaments may also occur and markedly impair motion. Occasionally, a gumma may break down and lead to an ulceration. A gummatous synovitis is also seen which very closely simulates a tuberculous process, and may be difficult to differentiate. The onset of the syphilitic type of the disease is more rapid, less painful, the effusion is greater and the lesion presents more symmetry. The Wassermann test is positive.

Chondro-arthritis commences by a fibrillation of the matrix of the cartilage and a proliferation of the cells. The cartilage becomes soft and is eroded by the friction of the articular surface. Pain is usually absent. The bone becomes pitted and these pits may be filled with caseous material.

Muscular System.

During the secondary stage of syphilis, myalgias are quite common. The pains are quite definitely localized, or they may be radiating in character. The lower limbs, loins and shoulders are most frequently affected. Contractions of some of the muscles may occur; the biceps is almost exclusively attacked, fixing the forearm in semiflexion—a condition which may last for several weeks.

In the tertiary stage, gummata may involve some of the muscles. The gummata are usually single and the sternocleidomastoid is most frequently affected. The tendon of a muscle may be invaded and lead to a rupture of the tendon. Diffuse interstitial myositis chiefly affects the biceps, the sphincter and the masseter and the flexors of the fingers, the deltoid or the sternomastoid. The onset is insidious; vague pains occur; progressive limitation of motion and a uniform swelling develops which produces pain on motion. The muscles slowly atrophy, become sclerosed, and an incurable deformity results. Amyloid degeneration also occurs.

Genito-urinary System.

BLADDER.—Gumma of the bladder may occur without symptoms, or it may produce symptoms, principally pain, which is variable in type, and may be intermittent, continuous or radiating and may be increased on pressure. These pains are especially marked at micturition, if the gumma occurs near the urethral orifice.

Hematuria is the most constant symptom of tertiary syphilis of the bladder. It is observed toward the end of micturition (terminal hematuria); or the blood may occur throughout the entire time of micturition and be either slight or profuse. The urine on microscopical examination, for the most part, contains a considerable number of blood-cells, both red and white. Pollakiuria is a frequent symptom. Gumma of the bladder is most likely to occur during middle life.

KIDNEY.—Gummata of the kidney are rarely recognized during life. The cortex of the kidney is most frequently involved, but invasion of the medulla may occur. Gumma of the kidney usually manifests itself a number of years after the initial lesion; it develops slowly, and rarely gives rise to symptoms which enable one to diagnose the condition. The gumma may, however, become very large and simulate malignancy. Chronic parenchymatous nephritis and amyloid degeneration are usually associated with this condition. Albuminuria is frequently observed during secondary syphilis but it also occurs in the tertiary stage.

Special Senses.

EYE: (*a*) *Gummatous Iritis.*—This condition may develop during the tertiary stage of syphilis. The ciliary border of the iris is the most common site. Gummatous iritis consists of yellow nodules which are similar to gummata in other parts of the body. This type of iritis when treated early usually responds readily.

(*b*) *Optic Neuritis.*—Gumma may produce optic neuritis. Venous congestion results and leads to hemorrhage upon the papilla, which is swollen. Unless antisyphilitic treatment is immediately administered, optic atrophy is likely to occur. The loss of vision is gradual and the field of vision becomes progressively decreased.

(*c*) *Paralysis of the External Ocular Muscles.*—The presence of a gumma may produce pressure on the nerves, which enervate the external muscles of the eye and produce a palsy or even a complete paralysis. The gumma may be located in various places in the brain, in the third or fourth ventricle, or in the region of the nuclei, or along the course of the nerve. The oculomotor nerve is most frequently involved and such involvement manifests itself through ptosis, bynopsia and strabismus. Paralysis of the third nerve is also followed by an enlargement of the pupil and loss of accommodation; and irregularity in the size of the pupils may result.

EAR.—The tertiary lesions of the ear are extremely rare. The auricle may be invaded by a gumma, and early and extensive ulceration may occur. The destruction is usually rapid. The external meatus is only rarely involved; deafness may occur at any time during the tertiary stage of syphilis. It usually has an insidious onset, and the patient is able to hear the voice for some time after he has lost the ability to hear higher tones. The most frequent cause is the presence of the gumma at the base of the brain, involving the auditory nerve.

Nervous System.

Syphilis of the nervous system occurs much more frequently in men than in women. It usually occurs between the ages of 25 and 40, and is most likely to occur following trauma, great nervous or mental strain. The nervous system, as a rule, does not become seriously involved if the syphilitic infection is diagnosed and treated early. It is the patient who does not notice the chancre or secondary symptoms, or else pays no attention to the presence thereof, who is usually thus affected.

SYPHILIS OF THE BRAIN.—The brain is quite frequently involved and about 50 per cent. of brain syphilis occurs within three years following the infection. It may develop much earlier. Syphilitic cerebromeningitis is probably the most frequent form of cerebrosyphilis. The favorite location for the lesions is the basilar area, but no part of the brain is exempt. In syphilitic meningitis, gummata are usually found which vary in size from miliary bodies to some of considerable size, which are either solitary, few or many. They act similar to brain tumors and produce similar symptoms.

SYPHILITIC LESIONS OF THE CRANIAL NERVES.—The cranial nerves are exposed at the base of the brain, where syphilitic meningeal involvement is most frequent. The thickening of the meninges is quite likely to compress the nerves as they pass out of the skull. The optic nerve, oculomotor, abducens, trigeminal, facial, auditory, and rarely the hypoglossus, glossopharyngeal and vagus, may be involved. The third nerve is affected in about 40 per cent. of the cases; it usually gives rise to ptosis, strabismus and pupillary stasis. Optic neuritis occurs very frequently and may lead to atrophy. The trigeminal, when involved, gives rise to disturbed sensibility, but more frequently to neuralgic pains. Facial paralysis is occasionally seen, and is sometimes associated with unilateral deafness.

The general symptoms of cerebral syphilis depend upon the lesions present and their location. There is nearly always a premonitory period during which treatment is of much value. Later the damage done to the brain is irreparable, and medication can do nothing more than check the progress of the disease. As a rule, brain syphilis first makes its appearance during the secondary stage, but it may occur at any time after that, even up to the twentieth or thirtieth year after the original infection. This premonitory stage is characterized by headaches which are severe and often deeply seated, as well as circumscribed. It is frequently marked by local tenderness on percussion and usually shows nocturnal exacerbations. Disturbance of sleep is also noted; this is due in part to the nocturnal headache, but the patient is often troubled with insomnia even after the headache subsides. The mental attitude of the patient is changed; he is apathetic, does not care to study or work, and his memory is frequently impaired; he feels and acts depressed and indifferent. His general health often fails, he loses in weight and becomes anemic.

SPINAL SYPHILIS.—Spinal syphilis usually makes its appearance between the third and sixth month after syphilitic infection, and is rather precocious. It involves the meninges, nerve roots and blood-vessels, and the symptoms depend upon the degree of involvement as well as upon the location of the lesions.

SYPHILITIC MENINGITIS AND MENINGOMYELITIS.—These furnish the usual type of spinal syphilis and are marked chiefly by pains which are of extreme intensity and usually much worse during the night. They are usually associated with the lower extremities, and pain in the back is also complained of. Palsies are usually partial and attack a certain group of muscles; they are accompanied by disturbed sensations in the cutaneous area of the identical innervation. Only rarely are palsies complete. The patient complains of a feeling of weakness in the legs and in rare cases the upper membranes are most affected. Frequently, the cord is affected and there is a tendency to spasticity in the lower extremities. Gummata in the meninges produce tumor symptoms or the Brown-Séquard syndrome.

SYPHILITIC ATAXIC PARAPLEGIA.—This condition is usually of insidious onset and develops within a few weeks, months or years. The first symptoms are a feeling of heaviness and paresthesia in the legs. These are soon accompanied by difficulty in emptying the bladder through the spasmodic action of the sphincter. Rigidity and spasticity of the legs soon develop and show themselves in the gait. The patient

drags his toes, his knees are adducted, and his steps become uncertain; knee jerks, the rectus and ankle clonus and the toe sign are usually well marked. Muscular strength is more or less reduced.

There is also a group of syphilitic infections for the so-called parasyphilitic disease, or syphilis of the fourth stage. Chief among these are *tabes* and *paretic dementia.* These diseases are fully discussed in the chapter on Syphilis of the Nervous System.

Laboratory Findings

Blood Tests.—Various tests have been devised to determine the syphilitic antibody in serum. The Wassermann test and its modifications are the tests most universally used.

WASSERMANN REACTION.—The Wassermann reaction, although it is known that it is not absolutely specific—since positive reaction is occasionally observed in other diseases than syphilis—yet the test indicates syphilis in a great majority of cases. Of tests done on 4,000 individuals suffering with other diseases than syphilis, Craig obtained 12 positive reactions (0.3 per cent.). These results now are attributed to errors in technic. A positive Wassermann test is considered clinical evidence of syphilis, except in the following: frambesia, the tubercular type of leprosy, some cases of relapsing fever, some malarial infections during the febrile stage, some instances of experimental trypanosomiasis, and beriberi. In all other diseases where the test was positive, it was impossible to rule out associated syphilis. In five cases of tertian malaria, Craig observed positive Wassermann reactions, and Thompson likewise obtained several positive reactions in the same diseases, but in each case the test became negative as soon as the fever and the plasmodium disappeared; yet the appearance of a positive Wassermann during this type of malaria is relatively rare.

Results of Wassermann Reaction in Various Stages of Syphilis.—The results of the Wassermann test, in the several stages of syphilis, vary considerably. The test is most frequently positive in the secondary stage, but primary and tertiary stages yield a high percentage of positive reactions. Craig has tabulated the results of the Wassermann test in 600 cases of syphilis. The following table is taken from his excellent work, "The Wassermann Test":

PRIMARY STAGE

Time of Appearance of Wassermann Reaction in 600 Cases of Primary Syphilis

Weeks after Appearance of Chancre	Total cases	Positive	Per cent.	Negative	Per cent.
First	77	27	36.3	50	64.9
Second	155	92	59.3	63	40.3
Third	158	109	68.9	49	31.0
Fourth	167	129	77.2	38	22.7
Fifth	43	35	81.3	8	18.6

Craig states that no test was considered positive unless there was complete inhibition of hemolysis (a ++++ reaction), except in very early primary cases, where a +++ reaction was considered positive in a few instances. Moreover, he states that in at least 95 per cent. of these cases only one Wassermann test was performed, and concludes that the percentage would undoubtedly be much higher had additional tests been made.

Time of Appearance of Reaction.—Craig observed, in 600 cases of primary syphilis, that 36.3 per cent. of the cases gave positive tests during the first week; 59.3 per cent. during the second week; 68.9 per cent. during the third week; 77.2 per cent. during the fourth week; and 81.3 per cent. during the fifth week. These figures show the great value of the Wassermann test, even in the primary stage of syphilis, and specially where it has been impossible to demonstrate the *Treponema pallidum* in the secretions. Cases are on record, moreover, which show that positive reactions have been obtained as early as the third and fourth day after the appearance of the chancre; also a few questionable cases where positive reactions were reported even before the initial lesion. Craig reports two cases which gave a positive Wassermann reaction five days after the initial lesion appeared and in each case *Treponemata pallida* were demonstrated. The number of positive tests obtained during the secondary stage, by a number of investigators, varies from about 80 to 100 per cent., with an average of about 94.5 per cent. In the tertiary stage, they vary from 57 to 96 per cent., with an average of 83.3 per cent. This seemingly great variation depends somewhat upon whether or not the patient has received treatment and the extent of the treatment. The results obtained by the Wassermann test during the latent stage of syphilis show a marked variation from 33.3 to 81 per cent., with an average of about 58 per cent., while in congenital syphilis the results vary from 60 to 100 per cent., with an average of 85.4 per cent.

The Wassermann reaction on the cerebrospinal fluid, during the primary stage, is rarely positive. Wile reports that 30 per cent. of the cases of secondary syphilis gave a positive Wassermann reaction on the spinal fluid. Craig and Collins also found that a considerable proportion of the early secondary cases gave positive reactions. In the tertiary stage, a considerable number of positive reactions were yielded, whereas in latent syphilis the percentage of positive reactions obtained is smaller and, according to Craig, does not exceed 15 per cent. Fordyce reports a pathological spinal fluid in less than 20 per cent. of the cases, with an absence of symptoms pointing to central nervous involvement.

Factors Which Influence the Wassermann Test.—There are several factors which influence the results of the Wassermann reaction, more or less, such as ingestion of alcohol in considerable amount, the development of certain bacteria in the blood serum, ether or chloroform anesthesia. There is also a variation in the strength of the reaction from day to day.

(*a*) *Ingestion of Alcohol.*—When large amounts of beer or whisky are ingested, a strongly positive serum can be changed to a negative one. The reaction generally becomes positive again within 24 hours, but may remain negative as long as three days. Nichols and Craig studied 9 cases, 3 of which were in the secondary stage and 6 in the tertiary stage of syphilis. Ingestion of alcohol caused positive reactions to disappear; in 5 of the cases, the reaction had become negative within one hour after the last dose of alcohol was administered, and all remained negative for several hours; 3 of the sera remained negative for 24 hours and in 1 case for three days. Experimental control showed that the reaction was not due to the alcohol itself, since much larger amounts were necessary to produce hemolysis, but that the alcohol probably rendered inert some of the substances in the blood-serum of the syphilitic, which bind the complement, thus causing a strongly positive test to become negative. It is possible that a weakly positive test may become negative after the ingestion of a small amount of alcohol. A negative test is of little or no value on a patient who has recently drunk any amount of alcoholic liquor.

(*b*) *Development of Certain Bacteria in Blood-serum.*—Certain anticomplementary substances may develop in the blood-serum of a patient and cause inhibition of hemolysis, both in tubes containing antigen and in the control tubes in the Wassermann test. As a rule, the majority of bacteria are destroyed by heating, but some of them may survive and thus interfere with the interpretation of the test by causing inhibition in the antigen and control tubes. Craig has shown that some of these anticomplementary bodies are produced by the growth of bacteria in the blood-serum to be tested, if the serum is kept for some time. The organisms do not only produce anticomplementary bodies, which cause inhibition of hemolysis in both the antigen and control tubes of the test, but certain species are shown to possess the power of causing inhibition of hemolysis in the antigen tube alone, thus producing a positive reaction in a serum which clinically should be absent. Thus, one sees the value of using fresh specimens of blood, wherever possible, and, if it is impossible to run the test soon after drawing the blood, the specimens should be collected with aseptic precautions, so as to prevent bacterial contamination, and the test made as soon as possible.

(*c*) *Ether or Chloroform Anesthesia.*—Occasionally, after a patient has had an ether or chloroform anesthetic, the blood yields a weakly positive reaction. To avoid a wrong interpretation of the test, a period of at least two days should be allowed to elapse, following anesthesia, before the Wassermann test is made on a patient.

(*d*) *Variation in Strength of Reaction from Day to Day.*—In the course of the examination of the blood-sera, variations frequently occur in which the reaction may vary from a strongly suspicious one to a doubtful or negative one within the period of a week or two. Rarely a positive test changes to a negative one, upon a second examination within a similar period, no treatment having been administered at any time; later tests again become positive. Such a phenomenon shows that there is an inherent error in the Wassermann test itself, due to a variation in the body or bodies of the serum which is essential to the reaction.

Value of Repeated Wassermann Tests.—Craig selected 10 patients suffering from undoubted syphilis, in order to observe the normal variation in the strength of the reaction in untreated cases of syphilis. Most of these men were prisoners and the use of alcohol was thus obviated. There were 2 in the primary stage, 4 in the secondary stage, and 4 in the latent stage of syphilis, no treatment having been administered for over a year. The patients in the primary stage had typical chancres; those in the secondary stage developed eruptions and mucous patches; while the four in the latent stage were free from obvious symptoms. All gave a ++++ reaction at the time of the experiment. Blood was collected every day and tested on the same day. Daily titrations of the strength of the complement-fixations were made.

In the primary stage, considerable variations occurred in the complement-fixing power of the blood-serum in both the cases, but in neither case did the reaction become negative with the diagnostic amount of serum—1/10 of 1 c.c. In one case, a slightly plus or doubtful reaction was obtained upon three of the seven days; in the other, on two of the seven days. This indicates that sufficient examination during the primary stage will lead to a higher percentage of positive results than are usually obtained.

In the secondary stage of syphilis variations were also observed, and it was noticed that a case giving almost complete inhibition of hemolysis on one day could be negative or doubtful on the succeeding day. In one case, the experiment gave a practically negative result on one day and a doubtful reaction on two other days. The four cases of latent syphilis gave a definite history of syphilis, but no symptoms were present for one year. All had received one to two injections of salvarsan and gave a ++ Wassermann reaction shortly before titration of the blood was begun. In three of the cases, the variation was very marked. In only one case was the Wassermann reaction definitely positive. These results show the fallacy of depending upon a single negative reaction for the elimination of syphilis. Repeated tests should be made before the patient is assured that he is free from syphilis, and then only when the results of the test are in accord with the history and physical findings.

PROVOCATIVE WASSERMANN TEST.—Gennerich, in 1910, first called attention to the fact that some cases of syphilis which gave repeated negative Wassermann tests gave a positive Wassermann reaction after the injection of salvarsan. He observed that the test became positive as early as a few hours after the injection or as late as two weeks following the injection. These results directed his attention to the value of the provocative Wassermann test in the diagnosis of syphilis, where the simple Wassermann was negative, as well as to its value in determining whether the patient was really cured of his syphilitic infection or not. He observed that the provocative Wassermann test was frequently positive in cases which had been treated for some time and which gave negative tests during a variable period. Milian, Herxheimer and Michaelis also called attention to the value of the provocative Wassermann test in studying syphilis.

The real value of the provocative tests is not as yet definitely established. King is very dubious about the existence of such a phenomenon. He believes that the change from negative to positive tests after the injection of salvarsan is due either to a normal variation in the complement-binding ability of the blood-serum or to variations in technic or from the reagents used in making the tests when the tests are made on different days. The work of many observers on the provocative tests does not corroborate his conclusions. In a series of ten cases Michaelis checked the provocative test with the luetin test, and in each case the tests agreed, proving conclusively that the phenomenon does occur. The exact cause of this phenomenon is not definitely known. Any of the antisyphilitic drugs are capable of producing the test, but salvarsan is the most effective. When mercury or potassium iodid is used, it is necessary to administer it for ten to fourteen days before attempting the test. Occasionally it is necessary to give three or four injections of salvarsan to produce a positive Wassermann reaction. This is especially true in cases of latent visceral syphilis.

Lerrede reports a case of syphilitic meningitis in which the test, which was negative, became positive after six injections of neosalvarsan and two weeks of rest, and also reports a case of tabes in which the provocative test became positive after four injections of neosalvarsan and a month of rest.

Two theories are offered to explain this phenomenal reaction. One of the theories considers the phenomenon as being the result of stimulation of the *Treponema pallidum* by the antisyphilitic drug, causing the organism to produce some substance which produces the Wassermann reaction; while the other theory holds that the reaction is the result of some substance or toxin liberated by the organism which stimulates the body tissues and increases the bodies involved in the Wassermann test. Since these changes may be only very temporary, it is necessary to withdraw the blood for the test very soon after the injection. Moreover, one test is not to be relied upon, if negative, but subsequent tests should be made at various times.

The technic of the test consists in taking blood from the vein before the administration of salvarsan for a control. The salvarsan is then administered, and a few hours later more blood is taken, and again at various subsequent times. The ideal method consists in withdrawing blood every four or eight hours during the first two days following the injection. In this way, the best results should be obtained. However, this method is hardly practicable. If possible, it is best to run as many of these specimens as possible at one time, since such procedure will reduce to a minimum the error in technic and that due to reagents. From .4 to .6 gram of salvarsan is the usual dose administered.

The percentage of provocative tests which result positive is comparatively small. Stokes and O'Leary obtained 19 positive tests in 103 of the provocative tests made—or 14.4 per cent. Craig's work is in accord with such figures and he states that very seldom are the figures higher than 20 per cent. obtained in a limited group.

A provocative Wassermann test is of value in recognizing syphilis in patients who have been free from symptoms for some time, thus determining that they are cured and need no further treatment, or that they are not cured and need further treatment. The provocative test is also of value in that large group of cases of old syphilis or suspected syphilis, which gives a + or ++ Wassermann reaction.

In cases of osseous syphilis, it was positive in 20 per cent. of the cases, while it was positive in 25 per cent. of cases with involvement of the central nervous system, and in 33 per cent. of vascular syphilis.

The indications for the provocative tests are very well summed up by Stokes and O'Leary. They consider the provocative test to be of value in:

(1) Cases with a definite history of primary or secondary lesions or suspicious genital sore of any description where the Wassermann is negative.

(2) Syphilis in the husband or wife or a history of a sore in either one.

(3) Treated cases to determine whether they are cured or need further treatment.

(4) Obscure bone or joint lesions.

(5) History of miscarriages unless the cause is obvious.

(6) Mothers of syphilitic children without clinical signs of the disease.

(7) Cases with a history of positive Wassermann elsewhere, negative on present examination.

(8) Mental deviates and constitutionally inferior individuals with suspicious histories.

(9) Certain signs, illustrated by special examinations, such as decreased bone conduction, with normal hearing, chorioretinitis, retinitis pigmentosa, bilateral dacryocystitis in childhood.

In spite of the fact of the small number of provocative Wassermann tests, which are positive in latent syphilis and syphilis of the bones and nervous system, we must consider it as a valuable diagnostic measure, inferior, however, to therapeutic tests. If the negative Wassermann reaction is to become positive, it usually does so within from a few hours to five or six days after the administration of the salvarsan. For this reason, it is good practice to take at least a daily specimen of blood for a week or ten days and again on the twelfth or fourteenth day.

HECHT-WEINBERG-GRADWOHL TEST.—The Hecht-Weinberg test, as modified by Gradwohl and carried out with a properly prepared and standardized antigen, furnishes a very delicate test for the detection of syphilis. The test is conducted with unheated sera and thus avoids the development of complementoid substances. Gradwohl states that the test has never been negative in any case where the Wassermann was positive, but that it has frequently been positive in cases where the Wassermann was negative. Heidingsfeld agrees in this statement. This makes the test especially valuable as a check on the Wassermann reaction. Even when the Wassermann test was conducted with the use of cholestrinized human heart antigen and the Hecht-Weinberg-Gradwohl test was conducted with the non-cholestrinized antigen, the latter test frequently gave positive results where the Wassermann test was negative.

Gradwohl, after an experience with 5,000 comparative Wassermann and Hecht-Weinberg-Gradwohl tests, was able to show that fully 98 per cent. of the people examined had some natural anti-sheep amboceptor present. This leaves approximately 2 per cent. of cases where the Hecht-Weinberg-Gradwohl is not applicable and where the Wassermann test would necessarily be employed. He considers it a far better test than the Wassermann in all cases, with the exception of this group. Kolmer, however, maintains that the Hecht-Weinberg-Gradwohl test possesses a greater negative than positive value, since it is open to the error of being falsely positive. He obtained about 4 per cent. pseudo-positive tests. These tests were done largely with the sera of healthy students and assistants, where the Wassermann was negative with all antigens, and the assumption was quite reasonable that they were not syphilitic. He obtained about 16 per cent. more positive reactions with this test than with the Wassermann when conducted with cholestrinized extract as antigen, of which reactions 12 per cent. were true positives, 26 per cent. more true positives when conducted with the alcoholic extract of liver, and 18 per cent. more positives when extract of acetone insoluble lipoids were used. Moreover, six of the sera examined by Kolmer produced positive Wassermanns and a negative Hecht-Weinberg-Gradwohl reaction, out of 360 which were examined—a figure slightly less than 2 per cent. He considers that the Hecht-Weinberg-Gradwohl reaction has its greatest value as a serological control in the treatment of syphilis, since during the treatment the Wassermann reaction becomes negative much sooner than the modified test.

Parasites.—*Dark Field Illumination.*—Schaudinn and Hoffman demonstrated the *Treponema pallidum* in primary and secondary lesions, by means of the dark field. To detect the *Treponema pallidum* in scrapings obtained from the chancre, smears from mucous patches, secretions of papules or condylomata, or even some of the secretions of the lymph glands, is now one of the means of establishing a definite diagnosis. Because of the great refractive power and the resistance which the *Treponema pallidum* offers toward staining with aniline dyes, it is not practicable to use ordinary bacterial dyes to demonstrate the organism. The use of the dark field illuminator is the best means of detecting the organism. With this apparatus, the organism is quite readily recognized. The use of an India-ink smear is also very useful in detecting the organisms. A drop of black India-ink is placed on a slide, some of the serum from the lesion is thoroughly mixed with it, and a cover glass placed over the smear.

Treponema pallidum is a very delicate structure, presenting from 6 to 12 or more spiral incurvations. The length varies from 3 microns in young organisms to 15 microns, with an average length of 7 to 8 microns. The width is about 0.25 to .4 micron. The organisms present rapid local movements, a double motion, with a resultant motion resembling a corkscrew. Its differentiation from other organisms resembling it is not very difficult; this is done by exclusion of diseases which are relatively rare in this country and by the difference in construction of the organisms.

In spite of the fact that the *Treponema pallidum* possesses rapid local movements, yet it does not travel across the microscopic field very quickly, but often remains in practically the same position for some time. This slow locomotion differentiates it from *Treponema gracilis* and *Treponema refringens,* which are the only two treponemata which are likely to be seen when searching for *Treponema pallidum* in the exudate from lesions other than those in the mouth. Besides moving faster, the *Treponema gracilis* is coarser, while *Treponema refringens* is much larger, thicker, and travels decidedly faster than the *Treponema pallidum.*

Tissue.—Biopsy as a means of diagnosing syphilis has long been practiced, but of late years it has been replaced by the Wassermann test to a great extent. There are, however, conditions in which its use is of great value. It is sometimes used to differentiate syphilis of the skin from tuberculosis of the skin, or a condylomatous growth or a malignant growth. A small section is removed by excision with a knife or scissors and is placed in a hardening solution for a short time; it is then placed on a slide and stained. Frozen sections are not easily prepared, because of the great difficulty in cutting so small a section with the microtome before it is somewhat hardened. After the section is prepared the histopathology is studied under the microscope and the diagnosis based on this.

HISTOPATHOLOGY.—In all syphilitic processes, irrespective of the stage of the disease, there is an accumulation of round cells and proliferation of connective tissue cells. This process is first observed in the region of the smaller blood-vessels, but later it is seen to extend to other tissues. The walls of the blood-vessels become thickened, and it is not uncommon to observe the presence of endarteritis.

(*a*) *The Primary Lesion.*—Primary lesions present areas of round-cell infiltration, first observed in the region of the blood-vessel; small spheroidal, epithelioid cells, with a proliferation of connective tissue cells in the neighborhood of the blood-vessels. Thickening of the endothelium of the vessels and rarely a giant cell may be observed.

(*b*) *The Secondary Lesions.*—The macular syphilid shows very few changes under the microscope. An erythema is present and the vessels of the papillæ and subjacent corium are dilated. There is an infiltration of lymphocytes and plasma cells surrounding these vessels. The papular syphilid shows as a circumscribed lesion in the cutis, composed of lymphocytes, plasma cells and fibroblasts. The blood-vessels show the characteristic changes seen in the chancre. Since the secondary syphilids undergo spontaneous involution, little more than a microscopic residue may be noticed.

(*c*) *Gumma.*—There is an extensive infiltration of round cells and a proliferation of connective tissue cells which are of a spindle type. The blood-vessels are considerably involved; the intima is thickened and the adventitia is also affected. Proliferation of new blood-vessels occurs; the center of the lesion is necrotic and may be replaced by a fibrous tissue. Giant cells occur, but are few in number.

ORGANISMS.—With proper staining, it is possible to demonstrate the *Treponema pallidum* in the tissue. The stains best suited for this are Goldhorn's stain, Gram's stain and Levaditi's. With stains by Goldhorn's method, the organisms present a violet color, which may be changed to a bluish-black by flooding the preparation for 15 to 20 seconds with Gram's iodin solution and washing it off, while by Gram's method the organisms assume a pink color. With Levaditi's stain, the organisms are dark.

Cerebrospinal Fluid.—Noguchi observed that in syphilitic infection and the so-called parasyphilitic infection there was an increase in the globulin content of the blood-serum and the cerebrospinal fluid. This is of great value, since it is more constant and more marked than the content in the Wassermann antibody. There are various tests formulated by Noguchi and Nonné which are used in determining the presence of globulin. Noguchi's test consists in using 2 parts of spinal fluid and 5 parts of butyric acid (10 per cent.) in a normal salt solution, heating them together over a flame and boiling for a short period; then 1 part of a normal sodium hydroxid solution is added, and the whole boiled once more for a few seconds. The appearance of a granular or flocculent precipitate indicates a positive test. Cerebrospinal fluid containing blood must be carefully avoided.

NONNE-APELT REACTION (PHASE 1).—A quantity of cerebrospinal fluid is layered over an equal quantity of a hot saturated solution of ammonium sulphate, by means of a pipet. The ammonium sulphate is first allowed to cool (one c.c. each of the fluid and sulphate is sufficient). If the globulins are increased, a more or less distinct ring occurs at the plane of contact. After this, the mixture is thoroughly shaken and the results estimated within 3 minutes. If the fluid is distinctly opalescent or cloudy, it is considered positive.

Besides determining the presence of globulin in the spinal fluid, it is also of value to determine the presence of lymphocytes. This is done with a counting chamber. A very slight lymphocytosis is commonly found in some of the syphilitic affections, such as general paresis, cerebrospinal syphilis and tabes dorsalis. It is less common, however, in tabes.

Nonne considers less than 6 cells per cubic millimeter normal; 6 to

10 cells per cubic millimeter as suspicious; and 10 cells per cubic millimeter of the spinal fluid as pathological.

COLLOIDAL GOLD TEST.—Lange, in 1912, discovered this test. In recent years it has been carefully investigated and shown to be peculiarly accurate in syphilitic cases and especially in paresis. It consists in mixing cerebrospinal serum with various dilutions of colloidal gold. Aside from the preparation of the colloidal gold solution, the test is extremely simple and can be carried out in from 5 to 10 minutes. The test depends upon various color changes; the color changes are entirely absent with a normal fluid.

Cutaneous Test.—The LUETIN TEST, first introduced by Noguchi, is a cutaneous reaction similar to the von Pirquet test for tuberculosis. Noguchi considers the test specific for syphilis and his work has met with more or less approval from other men. The test is made by injecting intracutaneously from 0.7 to .1 c.c. of luetin, which is a sterile emulsion prepared from heat-killed *Treponemata pallida* of various cultures. The results of the test are classed as positive or negative, and, according to Noguchi, the positive may appear in any one of three forms. It may appear (1) as a papular reaction, which makes its appearance within 24 to 48 hours following the injection; (2) as a pustular form, which is less frequent; or (3) a torpid form, which is characterized by the time of appearance, usually from 18 to 20 days.

A negative test consists of the absence of inflammation at the site of the injection or the disappearance of any existing redness by the fifth or sixth day. There are a certain number of cases, however, where it is very difficult to differentiate, clinically, a positive from a negative reaction. In such cases, any doubt can be readily removed by the use of biopsy and a study of the histopathology, such as infiltration of lymphocytes about the capillaries and the presence of giant cells.

The test is of most value in tertiary and latent syphilis and in the late secondary syphilis. Noguchi obtained positive tests in 80 per cent. of the cases of latent syphilis; 70 per cent. in cases of congenital syphilis; and 60 per cent. in cases of syphilis of the nervous system. The test is of little value in the primary and secondary stages of syphilis. The chief value of the test lies in diagnosing the occasional cases of tertiary, latent or congenital syphilis which do not produce a positive Wassermann reaction, and as a check on the Wassermann reaction.

The specificity of the test is, however, attacked by a number of recent investigators. Chieffi, after an extensive study of the test, concludes that it is not specific, shown by the fact that the reaction is frequently positive in non-syphilitic persons who have lupus, leprosy and other skin lesions, as well as by the fact that the reaction may be produced in syphilitic persons by the use of other toxic, bacteriological substances, such as gonococcus vaccines. Tzanch and Bernard, on the other hand, state that they obtained a positive test in a case of leprosy, but in no other cases. They further report that in six cases of hereditary syphilis the luetin test was positive in all six cases, whereas the Wassermann was positive in only three of them. Sherrick has shown that the luetin test is influenced by the ingestion of potassium iodid. He has been able to obtain positive tests by the administration of from 20 to 30 grains of potassium iodid, three times daily, irrespective of the presence of syphilis. The work of Lyon is in agreement with that of Sherrick. Sherrick was also able to obtain a reaction identical with the latent reaction, irrespective of the presence of a syphilitic infection by the intradermal injection of agar-agar, or starch, and the administration of potassium iodid. These results are in harmony with the work more recently done by Stokes, who was able to evoke a positive test by the intracutaneous injection of agar-agar, thus showing that the test was not specific. Stokes concludes that the reaction is a colloidal one and that, at least in part, the test is a physical reaction.

Special Examinations

X-ray Examinations.—Roentgen examination is of considerable diagnostic value in determining the presence of syphilis in certain cases which give repeated negative Wassermann reactions and in which the clinical picture is not quite clear.

BONES.—The examination of the bones by this method frequently reveals the presence of a syphilitic infection, characterized by rather definite pictures obtained on the roentgenogram, depending somewhat upon whether the infection is of the hereditary or acquired type. In hereditary syphilis, the most characteristic finding is the existence of osteochondritis. It manifests itself mainly as a periosteal thickening, with irregular absorption of the bones at the epiphyseal end of the diaphysis, a widening of the epiphyseal cartilage and irregular borders. In case of an epiphyseal separation a callous shadow occurs.

Syphilitic dactylitis usually involves the periosteal end of the diaphysis and leads to considerable thickening. These factors differentiate it from tuberculous dactylitis, which usually begins at the epiphysis and produces little thickening of the periosteum. Moreover, the swelling produced in tuberculosis is due to the inflammation in the soft tissues, while in syphilis the swelling is primarily the result of thickening of the bone itself. Tuberculosis is a destructive process, while syphilis is chiefly a productive process.

Ossifying periostitis is usually associated with syphilitic osteochondritis. It may be either unilateral or bilateral, and the flat bones are not infrequently affected. The acetabulum frequently shows osteophytic deposits; the ribs are practically always involved, concomitant with osteochondritis of any of the tubular bones.

The shadow of congenital syphilis is quite characteristic. There is an enlargement of the periosteum about the metacarpal bones or phalanges. The metatarsal or tarsal bones can be similarly affected. The shadow resembles a cloak enveloping the bone, and constitutes the characteristic picture.

The scabbard-shaped tibia is quite pathognomonic of hereditary syphilis. The shadow produced is that of a diffuse, spongy line-shadow which is usually enlarged; and frequently disintegration of the old bone may be noticed quite clearly. It is quite uncommon for other bones to be affected in hereditary syphilis, unless the tibiæ are likewise affected.

Acquired Syphilis.—Acquired syphilis manifests itself in the form of periostitis or gummatous periostitis and presents a periosteum with an irregular contour. Slight erosions may be present or an extensive ruggedness may exist. The periostitis may occur as scattered areas, or it may extend along the entire end of the diaphysis. The shadow produced is not always localized, but may be quite general in appearance. In case of a subperiosteal gumma, the periosteum may be distinctly elevated. The shadow produced will depend upon the location of the gumma; if placed superficially but little shadow will result. If the continuity of the periosteum is destroyed, the shadow produced will be distinctly moth-eaten in appearance. If the periosteum bulges considerably, a bow-like periosteum results, which occurs most frequently on the tibia. If a syphilitic osteitis is present, considerable hypertrophy exists and a roughness and furring is the result. Syphilitic invasion of the bone is always associated with sclerosis, which manifests itself by a darker shadow.

JOINTS.—Thickening of the periosteum is the most characteristic result of joint syphilis. On the roentgenogram the bones produce distinct shadows, quite different from those produced by tuberculosis of the joints. If sclerosis of the bone is present, a dark shadow located within a thin shadow is observed. This shadow is quite distinct, and is not spotted or irregular as in tuberculosis. Should any doubt exist as to diagnosis, a study of the lesions on the diaphysis, the result of an old periostitis, such as the sclerosis of the periosteum, and its thickening, will settle the diagnosis in favor of syphilis. The shadows produced by syphilis of the joints are similar to those produced when the shaft of the bone is affected. Syphilitic arthritis occurs in the form of a synovitis, with little tendency toward epiphyseal involvement, with no changes on the roentgenogram. A multiarticular form of syphilis of the joints occurs and manifests itself by swelling and flexion of the fingers, rarefaction and subsequent destruction of the bone ends, or bony ankylosis may occur.

Charcot Joints.—Charcot joints present a picture which varies with the progress of the involvement of the bones. It may present but a slight irregularity in the long outlines or it may be accompanied by complete destruction of the bones of the involved joint. Atrophy of the articular cartilage, irregular destruction of the bone, hyperplasia of bone and joint cartilage and translucent areas in the lower ends are often found.

THE AORTA.—Roentgen examination is frequently of the greatest value in diagnosis of difficult cases of aneurysm of the aorta. The characteristic finding is a diffuse dilation of the area, associated with a distinct bulging, which is more prominent than the rest of the vessel.

The roentgen finding depends upon the location of the aneurysm. When the ascending aorta is affected, the shadow produced by the dilated aorta contrasts very distinctly with the auricular shadow. When the arch is affected, a club appearance is noted, the result of a more prominent bulging on one side or the other. The descending type is characterized by a shadow which is rather transparent in its anterior portion.

Instrumental Examinations.—OPHTHALMOSCOPE.—Examination of the eye frequently furnishes considerable evidence for the diagnosis of syphilis. The eye is first examined externally to detect any asymmetry and the presence of ptosis or strabismus. This done, the pupils are carefully studied and any irregularities or changes in the size of the pupils noted. By the use of a small pocket light, held so that the rays of light do not directly enter the eye, the reaction of the pupils to light may be tested, noting whether they react rapidly, sluggishly, or not at all. The pupils are also tested for accommodation by having the patient look at some distant object for a short time and then look at the observer's finger or a pencil held quite close to the eye. If there is a change in the size of the pupils, the patient's pupils are still capable of accommodation. If the pupils react to distance and not to light, the patient has an Argyll Robertson pupil. This is very common in tertiary syphilis.

Internal examination of the eye should be made with the ophthalmoscope. With it, we are able to detect any changes in the fundus of the eye which are characteristic of syphilis. Findings with the ophthalmoscope vary according to whether the lesion is due to hereditary or acquired syphilis. Patches of pigment of various shades will be scattered over the background. The fundus is discolored, leaden, or brownish and reddish; yellow spots are noticed, standing out from the pigmented background. These spots may be observed at the periphery only and they are not necessarily very pronounced, but if at all prominent hereditary syphilis is indicated. Whitish, circular, and frequently confluent patches which appear to be located in the region of the choroid may be noticed. In acquired syphilis, the fundus is clouded and the disk appears red and hazy. White scales are frequently observed, which are quite characteristic and indicate disease of the retinal artery. Hemorrhages are not uncommon; or white lines occur which represent the circumscribed white exudate along the blood-vessel. There may be considerable deposits of pigment.

Iritis is the result of syphilis in about 25 per cent. of cases, and is an early symptom of the secondary stage. It is characterized by an immobile, slightly contracted pupil, which may be irregular; spots of exudate; dulling of the color of the iris; deep ciliary injection; pain and photophobia.

CYSTOSCOPE.—During the syphilitic infection, the bladder suffers along with the other epithelial and mucous tissue. Syphilis of the bladder may manifest itself entirely independently of other syphilitic manifestations and may consist of a simple hyperemia or actual gummatous destruction.

In the secondary stage of syphilis there is either an increased vascularization of the bladder mucosa or it becomes more or less congested. Diffuse islands of mucus are scattered through the mucosa, and in severe cases patches may occur which are identical with the mucous patches in the mouth. These may be multiple and become so extensive as to lead to ulceration.

In the tertiary stage, syphilis manifests itself as ulcerations or papillomata. Ulcerations are quite readily diagnosed; they may be rounded, rather extended, isolated or multiple; they may project into the cavity of the bladder; their edges are infiltrated, irregular, and the base is generally covered with a yellow, purulent mass. Occasionally, the syphilitic lesions appear as tumors, which are even pedunculated at times, and resemble very closely a polypus or a group of unequally enlarged papillomata. They are found in the region of the trigone, around the neck of the bladder and sometimes seem to be continued into the urethra.

LARYNGOSCOPE.—During the secondary stage, mucous tubercles or superficial ulcerations occasionally occur in the region of the vocal chords or on the epiglottis, at the same time as the skin rash and the condylomata and mucous patches occur in other locations. During the tertiary period, diffuse infiltrations or localized gummata may develop in the larynx, which produce destructive ulcerations. The epiglottis and aryteno-epiglottidean folds are especially involved, but the whole glottis may be affected. The perichondrium is quite likely to become affected and be followed by necrosis of the laryngeal cartilage. Cicatrization and laryngeal stenosis may be noted.

PROCTOSCOPE.—The proctoscope is a very valuable aid in detecting syphilitic lesions in the rectum. It is introduced gently into the rectum. The rectum becomes inflated with gas, and examination becomes relatively easy. This method is used to detect the initial lesion or primary chancre, which is occasionally found in the neighborhood of the anus, while in the secondary stage mucous patches or condylomata are sought, and in the tertiary stage the gummatous ulceration is the lesion looked for. Strictures may also be observed.

DIAGNOSIS

Since the prognosis of syphilis depends largely upon the administration of antisyphilitic treatment early, and since it becomes progressively worse as the *Treponema pallidum* is allowed to multiply within the body tissues, it is of the greatest importance that the diagnosis of syphilis be made as early as possible. The methods of diagnosis vary with the stage of the disease.

A. Diagnosis in Primary Stage

Diagnosis in the primary stage of syphilis is made by a study of the history, the examination of the patient, the finding of the organism by means of the examination of the exudate from the chancre, and by the complement-fixation test.

History.—The patient should be interrogated relative to his possible exposure to infection. The condition of exposure should be obtained, if possible, as well as the time of the appearance of the sore. The incubation period varies, but the chancre usually makes its appearance from 25 to 30 days following the infection; it may appear, however, as early as 14 to 17 days following the infection or as late as 40 days after the infection takes place. The *period of incubation* is of considerable value in differentiating the *syphilitic chancre* from *chancroid.* There is no such definite period of incubation preceding the appearance of the chancroid; it may appear a few hours to two days following the exposure; moreover, the syphilitic chancre is primarily a neoplasm, while the chancroid is of an ulcerous type. Unfortunately, many patients give a history which is very vague and of little value to the physician. If this is the case, it is necessary to ascertain as much as possible by examination of the patient.

Physical Findings.—Examination should consist of carefully observing the patient, who should be stripped. The lesion or lesions should first be observed and note should be made as to the location, number of lesions and the character of the lesions. This done, the glands of the groin, the epitrochlear glands, the cervical glands and suboccipital glands should be carefully palpated, in order to detect any enlargement. Enlargement of the epitrochlear glands is very suggestive of syphilis; it is, however, necessary to eliminate any enlargement which may be due to some other infection, such as infection of the hand, finger or forearm. Inguinal adenopathy in syphilis usually occurs within two weeks following the appearance of the syphilitic lesion and lasts from three to six months, depending upon treatment. The examination is not complete until the whole body has been carefully examined, paying special attention to the buttocks, the region of the anus and the mouth. The tongue must be very carefully examined, as also the mucous membrane of the mouth, the tonsils and the fauces. Although primary lesions in these areas are relatively uncommon, yet we cannot afford to overlook them if they are present.

Laboratory Findings.—EXUDATE FROM SORE.—After the lesion or lesions are located, an attempt should be made to demonstrate the *Treponema pallidum.* Serum from the sore should be collected and be examined by means of the dark-field illuminator. If the illuminator is not at hand, an India-ink stain should be prepared. The finding of the organism makes the diagnosis absolute. Frequently a patient who has used some antiseptic on the sore will present himself for examination. If this is the case, he should bathe the ulcer with plain H_2O and return in about 24 hours; examination at this time will reveal the *Treponema pallidum,* if present. If the ulcer does not ooze sufficient serum for examination, it can readily be made to do so by irritation, mechanically or chemically.

COMPLEMENT-FIXATION TEST.—The Wassermann test is of far greater value in making a diagnosis of syphilis during the primary stage of the disease than it is usually credited with. In a series of five thousand six hundred cases of syphilitic infection tested, Craig obtained a positive reaction in 89.8 per cent. of the primary cases; no cases were considered positive unless complete inhibition of hemolysis occurred, except in very early cases where a +++ blood test was considered as positive in a few instances. Moreover, only one test was made in over 95 per cent. of the cases. Had subsequent tests been made, the percentage of positive tests would undoubtedly have been greater. The time at which the Wassermann becomes positive during this stage is very variable; Craig reports 1 case where the Wassermann was positive 5 days after the chancre appeared and 2 cases where it was positive 8 days following the initial lesion. In about 36 per cent. of the primary cases tested, there were positive reactions during the first week following the initial lesion. Vedder reported 3 cases which gave a positive reaction 1 week following the appearance of the initial lesion, and in 2 of these the dark field examination was negative.

Noguchi in a series of cases of primary syphilis obtained 92.3 per cent. positive reactions, while Vedder in a separate series obtained 73.5 per cent. and 81 per cent. respectively. These results would lead to the conclusion that the Wassermann is of great diagnostic value in primary syphilis in a majority of cases, especially when it is impossible to demonstrate the *Treponema pallidum* in the exudate from the chancre, as is occasionally the case.

B. Diagnosis in Secondary Stage

The diagnosis of syphilis during the secondary stage is usually comparatively easy. It is based upon the history of the patient, physical examination and laboratory examination of the blood, spinal fluid, exudates and tissue removed by biopsy.

History.—The history of the patient should furnish us with the date of recent exposure or exposures, if this is possible. We should then inquire relative to the occurrence of a sore or sores; how long before healing was complete; when the sore was first noticed and the nature thereof. It is also necessary to inquire as to the occurrence of any adenopathy, especially in the inguinal region. We should also inquire relative to the occurrence of a rash; whether it was preceded by a sore or sores and the period that elapsed between the appearance of the sore and the eruption. The patient should be interrogated as to a sore throat, alopecia or peculiar cold sores on the lips. Further, his general health should be investigated, particularly as to fever, headache, bone pains, pains in the joints, and the general run down sensation commonly called "grip."

Physical Findings.—The patient should be stripped and his whole body carefully examined. His skin should be examined to detect any rash; his genitals should be examined to see whether there is any indication of an active sore or a scar, the result of its healing, and, if found, they should be palpated to detect any induration, and to determine its consistency. The groins, neck and epitrochlear region should be carefully palpated to discover any lymphatic gland enlargement, and the buttocks, anus and scrotum should be examined for condylomata. The throat should be examined for mucous patches, observing especially the lips, angle of the mouth, genitals, uvula, fauces and tongue.

THE RASH.—The rash, which occurs from 42 to 45 days following the appearance of the chancre, is the most diagnostic clinical sign of syphilis. The appearance of a rash with a rather definite incubation period following the initial lesion was depended upon formerly in making the final diagnosis of syphilis. Such procedure to-day would be unpardonable, since we have learned by modern experience that syphilis is more readily cured when it is treated early in the primary stage than after the secondary symptoms have appeared.

The rash begins as a macular eruption, which later becomes papular and even pustular. It begins most frequently on the sides of the chest, the flanks and the scapular region. It is at first relatively red, but later it becomes quite typical in appearance as regards color, location and morphology of the individual lesions. It assumes a copper color, which does not disappear on pressure; the flexor surfaces of the arms and legs, along with the soles and palms, the region about the mouth, nostrils and anus, are the sites usually affected. The papules may exfoliate, and thus each be topped by a small scale. This rash may be small or large, papular, pustular or even tubercular.

The rash is accompanied by more or less fever; the patient has headaches, which may be very severe and are most intense during the night. He has nocturnal bone aches, neuralgias, anemia, and, very frequently, splenic enlargement, and complains of a sore throat. Mucous patches are present in the mouth and may appear on any mucous surface. These are usually multiple and may even be associated with ulcerations. They are present fairly early in the secondary stage and are very contagious.

CONDYLOMATA.—Condylomata appear rather late in this period. They occur most commonly between the buttocks, in the region of the anus and about the scrotum, are flat and have a weeping surface. Like mucous patches, the condylomata are very contagious.

ALOPECIA SYPHILITICA.—Alopecia syphilitica affects the scalp, the eyelashes and eyebrows. The hair falls out in circular spots, which, however, are not entirely bald, but have stubs of hairs scattered over them. These spots may be numerous enough to give the scalp a peculiar moth-eaten or mouse-eaten appearance. The baldness is seldom permanent.

GLANDULAR INVOLVEMENT.—The lymphatic glands are extensively involved during this stage of syphilis. The involvement is very diffuse and is rarely followed by suppuration. Puncture of the large glands will enable one to obtain *Treponema pallidum* from the fluid so obtained.

THE EYE.—Examination of the eye is frequently of value in making a diagnosis of syphilis during the secondary stage. The infection produces an iritis and such a condition is equally as indicative of early syphilis as the Argyll Robertson pupil is of late syphilis. Internal examination with the ophthalmoscope may reveal the presence of a syphilitic retinitis or syphilitic choroidoretinitis.

Clinical Examination.—In the secondary stage, the general character of the eruption, its distribution on the flexor surface, its copper color and association with concomitant symptoms, along with history of an initial lesion, is usually sufficient to make a clinical diagnosis of syphilis. The finding of *Treponemata pallida* in the exudate from any of the lesions settles the diagnosis definitely. It is much more difficult to find the organism in such lesions as syphilitic papules on the skin, any ulcerations on the tonsils, palate, etc., than it is to detect them in the initial lesion. The detection of *Treponemata pallida* in condylomata, moist papules and mucous patches is relatively easy, as these lesions are very contagious and contain large numbers of *Treponemata pallida.*

To secure a good flow of serum, it may be necessary to remove the superficial epithelium to produce a fresh surface; then the serum is expressed from the lesion. Lieutenant Colonel L. W. Harrison (British) suggests a very efficient method of obtaining a secretion of exudate from syphilitic papules from the skin. The superficial layer of cells is first removed, the mouth of a test tube is then smeared with vaselin and the bottom of the tube heated; then the open end of the tube is placed over the denuded papule. Sufficient suction is produced to cause quite a flow of serum, which is collected and examined.

Laboratory Findings.—WASSERMANN TEST.—In the secondary stage of syphilis the Wassermann test is of most value as a diagnostic measure. Noguchi obtained 96 per cent. of positive reactions during the secondary stage; Craig, 96.1 per cent.; Vedder, 91.9 per cent.; and Swift, 92 per cent. Judging from such figures, we may readily conclude that the Wassermann reaction is a most certain diagnostic procedure during the secondary stage of the disease. If a negative Wassermann on the blood is obtained and the clinical findings point toward syphilis, a test should be made, using the spinal fluid, before syphilis is eliminated.

C. Diagnosis in Tertiary Stage

In many of the cases of tertiary syphilis the manifestations are very typical and the diagnosis is made easily.

History.—The characteristic lesions of this stage are tumors and ulcerations. Hence, our differential diagnosis deals mostly with differentiating tertiary syphilis from malignancy or tuberculous processes. The history of the patient should inform us as to any lesions of syphilis that have occurred at an earlier date, whether the patient ever observed an indolent sore—especially on the genitals—or a peculiar sore on any part of the body. It should inform us as to the previous occurrence of a rash, alopecia, sore throat, sores on lips or lesions around the anus. If any lesions are observed at the time of examination, the patient should be interrogated about the appearance, development and duration thereof, since the gummata which are the characteristic lesions of this period are relatively slow in developing and pursue a chronic clinical course.

Physical Findings.—It is on physical examination of the patient that we obtain most of our information for making a clinical diagnosis of tertiary syphilis. The patient should be carefully examined from head to foot, making sure no lesions which may be present may be overlooked. The gumma, the most characteristic lesion of this period, occurs on the lower limbs, the arms, head and cranium. The gumma first occurs as an oval nodule, quite deeply located in the subcutaneous tissue, and at first is small. The size varies considerably. The consistency of the gumma depends, however, upon the stage during which it is observed. It is quite hard during the period of development; later, it becomes softer and even ulcerates. Ulceration of the mucous membranes is very frequent, as is also sclerogummatous involvement of the tongue, with or without leukoplakia or ulceration. The palate is often involved and perforation may occur. Syphilitic periostitis is a rather common lesion during the tertiary stage of syphilis and it is the tibia which is most frequently involved, although none of the other bones are entirely exempt. Distinct bone changes take place with the formation of osteophytes. Osteosclerotic or osteoporotic changes develop occasionally. Not infrequently, the liver is involved by the infection, and such involvement is manifested by an increase in size, nodulation of the liver and jaundice. The vascular system suffers very severely at this time and may show itself in the form of arteriosclerosis, aneurysm, myocarditis and valvular insufficiency, infecting chiefly the aortic valve. It is frequently in the examination of the cardiovascular system that the first clinical hint of a tertiary syphilitic infection is obtained. Examination of the central nervous system is of great value, and often a diagnosis may be definitely established upon the findings obtained during such examination. The tendon reflexes may be abolished. The patient may have an Argyll Robertson pupil, which is very diagnostic of syphilis. The nervous symptoms produced are dependent largely upon the location of the gumma and are similar to those produced by a brain tumor.

Laboratory Findings.—EXAMINATION FOR TREPONEMA PALLIDUM.—The search for the organism in the exudate or scrapings of the tertiary lesions is usually unsuccessful; therefore, it becomes necessary to rely upon other laboratory tests to make an absolute diagnosis.

WASSERMANN TEST.—The Wassermann test is of considerable value in determining the diagnosis of tertiary syphilis. Craig found it to be positive in 87.4 per cent. of a series of cases of tertiary syphilis; Noguchi in 89.8 per cent.; Vedder in 86.3 per cent.; and Swift in only 80 per cent. A test should be made on the spinal fluid in all patients that have negative blood Wassermann reactions but in whom clinical findings point strongly toward the diagnosis of syphilis.

LUETIN TEST.—The luetin test is of value as a diagnostic measure for tertiary syphilis. The chief objection to the test is the inability to

differentiate a certain number of negative reactions from positive reactions.

X-RAY EXAMINATIONS.—The use of the *x*-ray, in carefully studying the bones of the body, is often a great aid in making a diagnosis of tertiary syphilis. The pathological changes in the bone, such as osteosclerosis, osteoporosis and other pathological lesions due to syphilis, are readily detected. Many times when the Wassermann test is negative, but the symptoms point toward syphilis, examination of the skeleton by means of the *x*-ray leads to a correct diagnosis.

Therapeutic Test.—At times all the data at our command for the diagnosis of syphilis are negative or uncertain and not in accord with the clinical findings. After carefully recording the patient's clinical condition, it is justifiable to place the patient on *antisyphilitic treatment,* watching him carefully and fully so that any effect produced by the treatment will be detected. If improvement takes place, a diagnosis of syphilis may be made.

D. Diagnosis in Latent Syphilis

The diagnosis of latent syphilis is often made with the greatest difficulty. This type of syphilis has no especial characteristics and we are forced to rely, to a large extent, upon the history of the patient, symptoms, and such physical findings as we may ascertain along with the various methods of laboratory diagnosis.

History.—It is necessary to ascertain from the patient, if possible, the previous existence of syphilis in any one of the three stages; also, an accurate description of the symptoms; and whether at any time he has taken antisyphilitic treatment, the period of treatment, and the nature thereof.

Physical Findings.—Physical examination may reveal little other than a characteristic scar, the result of a healing of a syphilitic lesion.

Pathological Changes.—Pathological changes brought about during the tertiary stage may be observed, such as bone changes, visceral changes and nervous involvement.

Laboratory Findings.—The WASSERMANN TEST is of the utmost value in latent syphilis. Craig obtained 68.1 per cent. of positive reactions, while Noguchi, Vedder and Swift obtained 77.7 per cent., 80.7 per cent. and 64 per cent. respectively. The test should always be used in conjunction with the clinical signs of syphilis when making the diagnosis. The Wassermann test on the spinal fluid should not be neglected and Lange's colloidal gold test and the globulin tests may be of great diagnostic value.

The clinical signs, together with the laboratory findings, must be considered as a whole before the diagnosis is made. In case the laboratory findings are not in accordance with the clinical findings, the therapeutic test may be employed and the response to treatment utilized in clinching the diagnosis.

DIFFERENTIAL DIAGNOSIS

Primary Stage.—The affections which are frequently confused or associated with syphilitic chancre of the genital organs are: herpes, chancroid, ecthyma, scabies, infected ulcers, balanitis, lichen planus, epithelioma of the penis.

Genital Herpes.—Genital herpes is characterized by groups of small vesicles on an inflamed base. Each group of vesicles is isolated. The vesicles tend to rupture early and then the lesion appears as a superficial ulcer covered with a reddish or brownish crust. These ulcerations may become somewhat indurated as a result of irritation and thus simulate the induration of the syphilitic chancre, but the induration is always much less marked than that of the chancre. The lymphatic ganglia may be affected by genital herpes, but the adenitis which accompanies it is less hard and more painful than that accompanying the syphilitic chancre. It is always somewhat painful to pressure and nearly always limited to a single ganglion. The course of the two affections is entirely different. The herpetic ulcerations heal readily in a few days, especially when located in a region which is not moist, or when secondary infection is prevented. Genital herpes is essentially a recurring affection, frequently accompanied with local burning. This recurrence is of value in the diagnosis, but does not exclude a syphilitic infection, since herpetic lesions may become secondarily infected with syphilis.

Chancroid.—The chancroid differs from syphilitic chancre in its irregular outline, its rugged surface, by the suppuration, or by the yellow exudate covering the lesions. Above all, it differs in the nature of its edges, which are undermined, sharp and are marked by a fine edge of yellow color, composed of necrotic tissue. This contrasts with the syphilitic chancre, which is without a real border. The base of the chancroid, which is sometimes indurated, is never as extensively indurated as the chancre. The chancroid is usually multiple, due to the fact that it is readily auto-inoculable. The condition of the lymphatic glands is variable. The adenopathy may be very extensive and the glands may suppurate, or there may be practically no glandular involvement. In the lesser degrees of involvement, the glands are painful only upon palpation or motion. In the more extensive involvements, with peri-adenitis, the glands become matted together into a tender mass adherent to the skin, which is inflamed. The glands are not painful; there is no periglandular exudate; and the skin is always movable over the mass. Examination of the exudate from the chancroid will reveal the presence of the bacillus of Ducrey. Another characteristic of the chancroid is its period of incubation. It appears within one, two or three days following coitus. Should the lesion appear less than five or six days after coitus, it is quite likely to be a chancroid. However, syphilitic infection may occur in the same lesion and we should make a practice of examining all genital sores that are at all questionable for *Treponema pallidum.*

Ecthyma.—Ecthyma of the genital organs is rare. The prepuce of the penis is the site most frequently attacked. A thick, grayish or brownish adherent crust covers the regularly rounded, distinctly excavated ulcer. The characteristic point is the existence of considerable suppuration under the scab. The base is not indurated, as in syphilitic chancre. Inguinal adenopathy of the inflammatory type is frequently present. Ecthyma of other parts of the body—especially the lower extremities—is usually present and helps to make the diagnosis.

Scabies.—The lesions of scabies, which have a marked predilection for the genital organs of man, most frequently produce small papules, covered with a gray crust, almost always surmounted with a ferrule, generally elongated, prominent and non-ulcerated. These lesions can be confused with chancre, but the presence of itching and scratch marks, together with the presence of lesions between the fingers, under the breasts, around the waist, and the absence of all lesions from the face and in the mouth make a diagnosis relatively easy.

Common Excoriations of the Genital Organs.—Common excoriations of the genital organs may become infected, due to lack of hygiene, and produce an inflammatory infiltration which simulates the indurated chancre. The outline is irregular and the edges are prominent, differentiating it from syphilitic chancre. Induration, however, may occur, but when wet compresses are applied for two or three days and irritation is avoided, all signs of inflammation disappear, showing that it is non-syphilitic.

Epithelioma of the Penis.—This condition is rare and occurs only in men of higher age. The lesion is irregular in outline and has a hard elevated border and base; often a bloody secretion is observed on the base. The woody hardness of the epithelioma is much harder than the infiltration of a chancre. The slow mode of onset and the progressive enlargement of the lesion over a period of weeks instead of days—as in the chancre—are characteristic features. The ulceration is deeper, the edges harder and the adenopathy, if present, is smaller and limited to the regional glands.

Balanitis.—(*a*) *Erosive, Gangrenous Balanitis.*—Erosive, gangrenous balanitis is a superficial ulcerative lesion, characterized by multiple, irregular and, at first, superficial erosions without induration in base or margins, rapidly producing extensive gangrene, even to complete loss of the penis.

(*b*) *Simple Balanitis.*—Simple balanitis presents an entirely different picture. It is characterized by diffuse map-like, very superficial ulcerations, surrounded by a markedly inflammatory skin and mucous membrane. There is complete absence of all infiltration. Adenitis is rare, but, if present, is moderate in size and inflammatory in type.

Lichen Planus.—This condition is mistaken for syphilis occasionally, because the flat umbilicated five-sided cutaneous papules, characteristic of the disease, commonly occur on the glans penis. However, there is no similarity at all between these lesions and a syphilitic chancre.

Secondary Stage.—There are a number of affections which must be differentiated from the lesions of secondary syphilis, such as scarlet fever, measles, pityriasis rosea, seborrheic dermatitis, tinea versicolor, ringworm of the glabrous skin, and eruptions following the use of certain drugs.

Scarlet Fever.—The eruption in scarlet fever frequently affects the region about the clavicles and rapidly spreads over the entire trunk, and a diffuse eruption also involves the extremities. It appears as a deep, cuticular flush which, however, differs in appearance from the involved skin of the roseolar eruption in syphilis. A raspberry tongue is also quite characteristic of scarlet fever. The onset of the disease is decidedly acute and is frequently ushered in with severe vomiting and a temperature, which rapidly mounts from 102° to 105° F. (38.9° to 40.6° C.)

Measles.—The fact that measles occurs more frequently in children than in adults is of diagnostic value, as is also the nature of the onset, which consists of general symptoms, such as fever, nausea, catarrh, bronchitis and running at the eyes. The eruption is distinctly eruptive in nature, much more so than the syphilitic eruption. The site of the eruption is important. Measles attacks the face quite extensively, whereas in syphilis it is the sides of the chest, flanks and scapular region which are most frequently involved. The finding of the bluish Koplik's spots on the mucosa of the cheeks is a diagnostic point in favor of measles.

Pityriasis Rosea.—Pityriasis is quite frequently confused with the lesions of syphilis. The reason for this is because the character of the rash in pityriasis is not generally recognized; not because of the great similarity which exists between the two conditions. There are two conditions which, if borne in mind, will usually obviate any difficulty in differentiating the eruptions. These are (1) the appearance of medallion-like lesions, of which the larger are two or three centimeters wide and the smaller 8 to 10 millimeters; and (2) the scaling. The medallia have a small elevated border, which is reddish and appears as a branny scale. The center of the medallion is the color of chamois, and it presents a slight folding parallel to the lines of cleavage and scales, and with a tendency toward central clearing as the border advances. The long axis of the lesions is at right angles to the vertical axis of the body; there is no lymphatic enlargement, as occurs with the syphilitic rash.

Seborrheic Dermatitis.—This is characterized by much itching, particularly when the patient is perspiring. It has a light appearance and affects, chiefly, the scalp and face. The scales are heavy, yellowish in color, and thick and heavy.

Tinea Versicolor.—Tinea versicolor, as a rule, presents no great difficulty of diagnosis, when the characteristic fawn-colored spots occur. However, the lesions at times are reddish in color, but even then they have the characteristic scale which is readily removed and, upon examination, shows the fungus.

Ringworm.—Ringworm of the skin presents circular lesions. They are few in number, are elevated, and the inflamed border is frequently covered by small pustules. The lesions are larger than those of syphilis. They scale and usually itch. Microscopical examination shows the characteristic fungus.

Eruptions Following Use of Certain Drugs.—Lesions of the skin which resemble syphilis may be produced by the use of certain drugs, such as copaiba and antipyrin. The presence of the itching, along with a consideration of their location, and their disappearance upon the discontinuance of the drug are usually sufficient to establish a diagnosis.

PAPULAR LESIONS OF SECONDARY STAGE.—Psoriasis, acne vulgaris, lichen planus, impetigo contagiosa and eczema may be confused with the papular lesions of secondary syphilis.

Psoriasis.—The papules of psoriasis commonly are present on the extensor surface of the knees and elbows, over the sacrum and on the scalp. The psoriases-form syphilids are usually lenticular, destructive, and have a predilection for the palms and soles. The scales of psoriasis are abundant, thick, imbricated and silvery white, while the scales in syphilis are small, gray, and frequently form a circle about the lesion. The syphilitic lesions are more indurated and bleed more readily when the scales are removed.

Acne Vulgaris.—Acne vulgaris must frequently be differentiated from acneform syphilids. Acne vulgaris occurs most commonly over the shoulders, the upper part of the chest and the forehead; while syphilids are scattered quite diffusely. Acne vulgaris is a purely chronic condition, and lesions of all ages are present; papules, pustules, comedones and even cicatrization may be present, while the syphilid is usually of one form only. Moreover, the lesions in acne vulgaris are decidedly hard, indurated and inflamed.

Lichen Planus.—This condition may be confused with the lichenoid type of syphilid. It usually occurs, however, on the flexor surface of the forearm, the wrist, and upon the inner aspect of the thighs, while the lichen syphilid is most frequently found on the back. The syphilitic lesions are more indurated and usually there is no itching. The lesions are circular in outline; they are acuminate and closely grouped. Lichen planus is characterized by papular lesions, which are polygonal in shape, have a flat surface, are umbilicated and of a violet hue.

Impetigo Contagiosa.—Impetigo contagiosa simulates the type of syphilid which is crusted. The lesions in impetigo contagiosa are round, yellow and present a crust, which appears to be glued to the skin and which has a porous appearance. When the crust is removed, the skin is noticed to be moist and reddish in color, without induration. The finding of *Pediculi capites* helps in making the diagnosis, since *Pediculi capites* and impetigo contagiosa are so frequently associated. The syphilitic lesions have a tendency toward coalescence, with the formation of plaques, which is seldom the case in impetigo contagiosa. Upon the removal of the crust of the syphilitic lesion, an indurated papule is

observed. This is of decided importance in making the diagnosis of syphilis.

Dry Eczema of the Palm.—Dry eczema of the palm and palmar syphilids are frequently differentiated only with great difficulty. Eczema most frequently affects the palms of both hands, while syphilitic lesions usually involve only one palm. The palmar syphilid shows well-marked induration and has a well-marked, slightly elevated, circumscribed border—all of which are less marked or absent in palmar eczema. Eczema has a tendency to affect the dorsum of the hand, while syphilitic affections do not tend to spread, and usually affect only part of the palm. Vesicopustular lesions of eczema are very much inflamed, irregular and crusted. They develop in a few days, while syphilids require a few weeks to develop, are regular, not inflamed, but moderately indurated.

NON-ULCERATED TUBERCULAR SYPHILIDS.—*Lupus Vulgaris.*—Lupus vulgaris must be distinguished from the non-ulcerated tubercular syphilids. It usually begins very early in childhood and its progress is relatively slow. The lupus vulgaris nodules usually manifest little or no elevation. Examination with the diascope usually reveals the apple-jelly nodules characteristic of lupus vulgaris.

Acne Necrotica.—Acne necrotica usually affects the forehead, chiefly along the hair line, but other portions of the scalp are affected as well; also the sternum and scapulæ. The affection begins as a vesicopustule. The lesions are hard, inflammatory, irregular and less indurated than the syphilids.

Tertiary Stage.—*Benign Tumors.*—Some of the benign tumors, such as lipoma fibroma and sebaceous cysts, may be confused with gumma during the process of development. These lesions are chronic and their development is quite different from that of the gumma, when they break down and suppurate. They do not possess the characteristic gummatous appearance.

Sporotrichosis.—The lesions in sporotrichosis develop rather rapidly and are quite numerous. They do not attack the lower extremities as frequently as the gummata. When they break down a small lesion results, the borders of which are irregular, undermined and violaceous. The core is not present. Auto-intoxication is frequent; pain, fever and enlargement of the lymphatic glands occur, but the ulcer usually heals rapidly after excision.

Tubercular Abscesses.—These frequently occur in the region of the neck and are usually secondary to bone involvement. They develop slowly and possess no core. The borders are irregular, the edges undermined and the ulcers appear of a dark red-violet hue.

Carcinomatous Ulcer.—Carcinoma is characterized by early glandular involvement, with adherence to the skin—quite different from the gumma, which does not cause glandular involvement and becomes adherent to the skin rather late. The edges of the carcinomatous ulcer are irregular and decidedly hard. The ulcer bleeds easily and there is a fetid, necrotic discharge.

Varicose Ulcer.—Varicose ulcer presents, not infrequently, considerable difficulty in differentiating it from the gummatous ulcer. It usually occurs on the lower half of the leg, whereas syphilitic ulcer occurs on the upper half. It is usually single and more irregular than the gumma; several gummata may occur at one time. The base of the varicose ulcer may be reddish, yellow, gray or even violet; it may be covered with a purulent secretion. The borders of the varicose lesions are thick, elevated, the sides slope, and it does not present the punched-out appearance of a gummatous lesion. Varicose ulcers may be surrounded by an edematous, pigmented zone, which may involve the greater part of the limb. There is practically no crust in the varicose ulcer, while that of the syphilitic gummata is thick, stratified, dark brown and very adherent. Varicose veins are present in the leg above the varicose ulcer.

Clinical Varieties

Syphilis made be of various types. It may run a mild course, or it may be of a very malignant nature. It is impossible to definitely classify the various cases of syphilis, but the following outline will be found to include practically all cases.

(1) **Mild Early Syphilis.**—This type of syphilis is most likely to be observed in strong, healthy, young individuals whose habits are good and who pay special attention to hygienic conditions. The syphilitic who notices his chancre early, consults his physician for advice and treatment and then carefully observes the advice relative to rest, exercise and abstinence from excesses, and who receives the proper kind of treatment is very likely to run a mild course.

(2) **Malignant Early Syphilis.**—Patients with a much lowered resistance and who pay little attention to personal hygiene and habits are most likely to suffer with severe type of syphilis when infection occurs. This is especially true if the infecting organism is of a virulent type. The patient may neglect treatment, or the treatment may be inadequate; he may run a fever and lose weight rapidly. Malignant secondary syphilis is very frequently followed by a severe ocular trouble and also by paralysis.

(3) **Persistent Syphilis.**—The syphilitic infection usually persists for some time, in spite of antisyphilitic treatment; but in the majority of cases such syphilis runs a fairly mild course. The patient responds to the treatment gradually, but not readily. This is especially true, when some intercurrent disease is present, or where the patient's tolerance for the treatment is not sufficiently high. He may be ill for a considerable time, but usually if his living conditions are carefully attended to and a better or more persistent treatment administered he gradually recovers.

(4) **Relapsing Syphilis.**—Cases which are poorly or not at all treated are most prone to relapse. However, syphilis may recur, even with proper treatment. Frequently, the patient takes sufficient treatment, becomes apparently free of syphilis and then discontinues treatment. The relapse of syphilis in such cases is quite likely. Moreover, he may

become more or less careless in his mode of living, indulge in excesses, and lower his resistance to such an extent that the body is unable to cope with the disease and destroy the *Treponema pallidum.*

(5) **Late Malignant Syphilis.**—Occasionally, the syphilitic infection may run a comparatively mild course for some time and then be followed by such conditions as tabes or by gummatous invasion of the bone.

(6) **Mild Late Syphilis.**—When a relapse occurs during late syphilis, it is relatively mild, in the majority of cases. Such relapse usually manifests itself as local lesions which readily respond to treatment. It is in this type of case that we observe the chancre redux, or the relapse may manifest itself as a lesion on the tongue or by the development of a periosteal node.

TREATMENT

Prophylaxis

General Prophylaxis.—Because it obliterates preputial folds and pockets, **circumcision** will protect the individual from syphilitic infection to a greater or less extent; consequently, circumcision is of decided value as regards the prophylaxis of syphilis and chancroid. The **maintenance of extraordinarily good physical health** at all times has some slight preventive value, but not as much as such a physical state has in many other diseases.

The chief and best means for the prevention of syphilis is the use of local agents that are destructive to the life of the *Treponema pallidum;* namely, **soap solutions, mercurial** and **arsenical preparations**—particularly **calomel in lanolin.**

Calomel, 33 per cent. in lanolin, as a syphilitic prophylactic, was brought out by Metchnikoff and proved by him to be of great benefit in the prevention of syphilis. This is one of the most brilliant pieces of research work with which the author is familiar. Metchnikoff shows the protective value of calomel in lanolin to be absolute up to 18½ hours after inoculation; from this hour on, the results are uncertain.

Major Reasoner has shown that **weak solutions of soap** are very deadly to the *Treponemata pallida.* This is very interesting to the writer, as for many years he has been teaching a method of protecting the doctor's fingers from syphilitic infection while making rectal or vaginal examinations, by the use of soap, to fill the space beneath the nail and the nail fold, thus covering the examining finger with a thin layer of soap. The use of soap was advised because it was easily obtained and made a covering—a mechanical protection, as it were—which was easily removed by cold water when the examination was completed. At that time, the author had no idea that soap was such an active spirocheticid. The *Treponemata pallida,* when mixed with a solution of soap that is so weak that it will not solidify, are practically instantly killed and their bodies disintegrated. Major Reasoner's experiments prove that *Treponemata pallida* placed alive in a solution of soap of a considerable degree of dilution, such as a lather used in shaving, immediately die when brought into contact with it. Consequently, one of the very best protective measures against syphilis is a thorough lathering of the exposed part with soapsuds, leaving the soap in place for from five to ten minutes before removing it.

Physicians and Nurses.—Physicians and nurses, when handling known syphilitic lesions, should protect themselves by avoiding contact with secretions that are likely to contain *Treponemata pallida.* If they must touch lesions known to contain *Treponemata pallida,* their hands should be protected by **rubber gloves,** by **calomel salve, mercurial salve** or **soap.** Nurses should be taught that any ulcerative or condylomatous lesions about the mouth and genitals, of whose character they are not certain, should be treated, as far as their personal prophylaxis is concerned, as if they were syphilitic lesions.

Individual Prophylaxis.—The patient should be told that he must not kiss any one and that he must **abstain from all personal contact** of any sort, until such time as his physician declares him to be non-infectious. He should have his own personal dishes and silverware; or, better, his dishes and silverware should be boiled for five minutes after each meal. To determine the infectiousness of a patient, we should **examine** him **carefully for lesions,** particularly around the lips and mouth and around the genitalia. If his Wassermann is negative, and we find no lesions whatsoever on his lips, tongue or inside of the mouth, we may feel reasonably certain he will not convey the disease to any one by mouth contact.

General Management

General Hygiene.—The diagnosis of syphilis should be made beyond the question of doubt. After the diagnosis of syphilis, the patient should have a **complete physical examination.**

Particular attention should be paid to the condition of the **teeth and gums;** the examination should be exhaustive as to the presence or absence of **deposits of calculus on the teeth** and the presence of **pyorrhea.** The mouth and tongue should be thoroughly **examined for any lesions,** due to the presence of old roots of carious teeth and irritated areas caused by defective dental work, such as bridges, crowns, etc. **Any defects** discovered **should be corrected;** if not at once, as soon as the greatest danger of infection has passed. The mouth should be put in first-class condition, as the remedies used in the treatment of syphilis, as well as the toxins of the disease itself, are irritant and destructive to the gums and peridental tissues. Consequently, any previously existing but slight disease of these structures is markedly aggravated when these tissues have the added irritants of syphilis toxin and mercury to combat.

The mucous membrane of the mouth has to withstand the assaults of the disease, and if we use mercury in the treatment of the disease, it is subjected to further irritation from the mercury. For this reason.

before the patient is treated, his **teeth should be cleaned and attended to by a dentist.** If this is not considered feasible before treatment, it should be done after the first or second novarsenobenzol injection has been administered and the lesions of the mouth have been healed, consequently diminishing greatly the risk of infection to the dentist's fingers. The patient should be given **weak solution of a scented, perfumed soap,** to use upon his teeth, or a **weak solution of chlorate of potassium**—about one-half teaspoonful in a glass of water.

The **tonsils and fauces should be observed** and the presence or absence of lesions in the crypts of the tonsils determined. If there is any retained material, this material should be expressed as soon as feasible.

The **urine** should be subjected to a **routine examination** for sugar, albumin and casts before any treatment is begun, so that we may modify and adapt the treatment to the individual in such a manner as is best suited to conserve the function of any organs previously diseased. The **blood-pressure** should be taken and the condition of the **eyes and nervous system** determined by a short routine examination. As a general rule, all remediable conditions should be remedied before we start on the routine treatment of a syphilitic individual.

As a matter of practice, when we have an individual in the florid stage of syphilis, highly infectious, many times it is better practice, both for the individual and for those concerned in correcting the defects, to **postpone the correction of these conditions** until we have by treatment decreased the contagion. This is particularly true in regard to lesions of the mouth, gums and throat. If pyorrhea or salivary calculus is present, no one would care to work upon the mouth of such an individual in the florid stage of syphilis. A few **arsenical treatments** will heal up the lesions sufficiently to allow the necessary dental work to be done before it is necessary to administer much mercury to the patient.

We should remember particularly that it is necessary, above all, to **consider the individual** and **not only the one disease.** The individual may have intercurrent diseases while he is being treated for syphilis and he may have other diseases present at the time that the diagnosis of his syphilis is made; and these diseases should receive appropriate attention. If a syphilitic treatment should tend to aggravate these complicating diseases, one of the other methods of treatment of syphilis should be employed. During the course of a routine treatment for syphilis, the **general health** of the individual **should be maintained** at or above normal; he should not be poisoned with the treatment, but, on the other hand, we should give him sufficient treatment so the disease will not bring down his general health.

In striking a balance between the toxemia of the disease and that of the treatment, one should use his best clinical judgment. The test as to the correctness of the course pursued is the improvement of the general condition of the patient. If he feels stronger and has a general feeling of good health, we know then that our course is correct.

and it should be continued. If this condition of good health does not prevail, something is radically wrong with the treatment; the treatment is either too vigorous or it may be insufficient.

If the treatment has been insufficient the symptoms, such as anemia, general grippy feeling, headache and depression, will still be present or only partially relieved; the objective syphilitic lesions will be not at all or only slightly affected. If we have the other extreme and have given the patient too much treatment, the patient's clinical condition will be the same as before, while the syphilitic lesions will have been much benefited, or completely healed, but still the patient's general condition does not improve; he loses weight, he is thin, tired, complains of loss of appetite and in many ways his general physical condition is unsatisfactory. Under these circumstances, we should **decrease or completely suspend treatment** for a time.

Tobacco.—Hygiene in the treatment of syphilis is extremely important. Tobacco has a markedly deleterious effect upon the lesions of the mouth, and tends to aggravate mucous patches, if present, and develop them if they are not present. However, the effect of tobacco on the general course and symptoms of the disease other than in the mouth is not of much importance unless indulged in to the point of marked intoxication.

Alcohol.—Alcohol has no direct local effect on any of the syphilitic lesions, but an individual who is a chronic drinker—never drunk but more or less saturated with alcohol most of the time—is sure to be a bad risk and his syphilis is certain to run a much more severe course than one who is a total abstainer; hence, our rule as to alcohol is to allow the moderate drinker—who drinks only with his meals—his appetizer, his beer or his wine, but to forbid any drinking at other times.

The syphilitic individual should undergo a course of physical training, consisting of **regular exercise, moderate diet, regular hours, regular rest** and a **minimum of work.** This régime should put him in the finest physical condition and should be persisted in for at least the first six months of his treatment; better still, throughout the entire course.

Diet.—The diet of the patient with syphilis should be abundant and simple. He should take **no acids** and **no acid fruits or vegetables,** such as oranges, lemons, grapefruit, tomatoes, rhubarb, strawberries or any other fruits containing a small amount of acid. This prohibition of acid is absolute when the patient is taking mercury in any form, or in any manner, but during the mercury rest period, or while he is taking arsenic only, he may have such of these acid fruits as he desires.

While he is **taking mercury** he should **avoid any foods that** have a tendency to **irritate the bowel** or to cause diarrhea, as the bowel—and particularly the caput coli—is easily irritated by the mercury; and any lesions in the bowel, due to improper or irritating foods, will be aggravated by the mercurial medication.

Local Treatment

There is a tendency to neglect local treatment of syphilitic lesions, because the constitutional treatment of them is so effective, but syphilitic ulcerative lesions will heal much more readily if **proper local treatment** is applied than if we depend entirely upon the constitutional treatment.

For the chancre, we apply **mercury** locally, either in the form of a salve (unguentum hydrargyri); or a solution of mercury bichlorid, 1:1000; or lotio nigra (calomel grains 4 [0.25 gram]; lime water 1 ounce [30 c.c.]). **Salvarsan or Neosalvarsan** can be applied locally, either in the form of a powder or in a 10 to 15 per cent. solution in glycerin. The local lesions on the lips, cheeks and tongue should be treated in the same manner, applying the mercury solution, the salvarsan solution, or using the old, well-tried **cautery stick of nitrate of silver.**

In the *primary or early secondary stage* of syphilis, the chancre is the only lesion present that contains any amount of fibrous exudate. This exudate protects the *Treponema pallidum* from the destructive action of antisyphilitic remedies; consequently, if we **remove the chancre surgically** or destroy it completely by local use of destructive methods, as **nitric acid, hot cautery iron, fulguration or the infiltration of the chancre with bichlorid solution,** we tend to prevent relapses from reinfection, as all the infiltrated tissues of the chancre with its contained *Treponemata pallida* are destroyed. This destruction or removal of the chancre has no effect whatsoever upon the immediate course and progress of the disease.

In the *tertiary stage* of syphilis, where there is considerable destruction of tissue, the **necrotic tissue** should be **removed mechanically** with the knife, scissors and tissue forceps. All crusts, scabs and dried secretions should be removed at the time of the inception of constitutional treatment and their re-formation prevented as much as possible by means of frequent **change of dressings** and the use of **local washes.** If this is not done, the local healing will be much delayed.

Hydrotherapy

The idea that the waters of certain springs exert a true specific effect upon syphilitic lesions is no longer maintained; but the usefulness of such waters as adjuvants to the treatment of syphilis is well recognized by every one. Their effects are produced by the combined action of several factors: When they are taking these waters, patients are away from home and are giving their time, thought and attention to the treatment of the disease; there is medical surveillance, and the general hygiene as to diet, exercise and rest is of the best. Some of these waters are slightly radio-active and these minute amounts of radium act as stimuli to the cellular metabolism. The sulphur waters and particularly those that contain, in addition, sodium chlorid, are reputed to enable the patient to tolerate much larger doses of the specific medication than he would otherwise be able to take.

This *increased tolerance to mercury* is probably due also to the fact that the patient while sojourning at any of these springs drinks, by the clock, a certain specific amount of water at certain definite times, and in this way his total intake of fluid for twenty-four hours is much increased, thus diluting whatever toxins are present in the body and enabling the inunctories to eliminate a much larger amount of the mercurial salts. Rarely can a patient, while attending to his ordinary business, tolerate rubs of more than a dram of mercurial ointment once daily. When he is under hydrotherapeutic treatment, consisting of warm baths and massage daily, and doing no work, and resting practically throughout the entire day, he can tolerate from two to three drams daily as an inunction.

The sum total of the hydrotherapeutic measures, the rest and the regularity of food and régime, show that they are undoubtedly extraordinary aids to mercurial or arsenical treatment of syphilis; and when these conditions obtain, syphilitic lesions heal much more rapidly than without them.

Constitutional Treatment

The drugs necessary for combating syphilitic infection are few in number: **mercury, iodid, arsenic, tonics.**

The preparations of these drugs and the methods of applying them to the particular case at hand, are extremely numerous and varied. We have learned by an extended clinical use of these drugs that certain drugs, and further, certain preparations of these drugs, are very potent in treating some syphilitic lesions, while other lesions are extraordinarily resistant to these preparations but yield readily to the same remedy in a slightly different form or administered by a different route.

In using remedies to combat syphilis, it should be borne in mind that whatever drugs are used should be **pushed to the physiological limit.** The drugs should be given in as large doses as the patient can tolerate without interfering with his general health, and maintained at this point for months. Throughout the entire time of administration of any drug to the patient, the **patient should be regularly and carefully observed,** so that one can immediately note any signs of breakdown in his general physical condition, such as gingivitis, loss of weight or appetite, or stomach or bowel trouble. If any of these symptoms occur, the drugs should be stopped at once or the daily dose gradually reduced and appropriate measures taken to combat the complication immediately.

Mercury.—Mercury, the old therapeutic standby, which for many years has been the chief remedy with which we combated syphilis, may be administered in many ways:

(1) Mouth: Ingestion
  Inhalation
(2) Endermic: Salve
  Pads
  Fumigation

(3) Intramuscular: Insoluble
Soluble preparations
(4) Intravenous
(5) Rectal: Suppository
Salve

(1) Mercury by Mouth.—Mercury by mouth may be administered in the form of a solution, pills, capsule, powder, or mixed with iodid.

(*a*) *Solution.*—Mercurial solution by mouth is usually administered in the form of a simple watery solution, or these solutions may be flavored by using any of the pharmacopeial syrups as vehicles. The bichlorid is the most suitable mercury salt for use in solution because of its universal availability and its solubility, although any of the other soluble salts of mercury may be used. The bichlorid is given in doses of grains 1/30 to 1/15 (.002 to .004 gram), three to four times daily, well diluted in water, or better, in milk. There is sufficient albumin in milk to change the bichlorid into the non-irritating albuminate of mercury, or we can prescribe the albuminate of mercury directly by using a small amount of egg albumen or blood-serum in the prescription with the bichlorid. Bichlorid is frequently given in combination with potassium iodid in the form of a solution. This is the so-called mixed treatment. An effective and palatable combination is as follows:

℞
Hydrargyri chloridi corrosivi...........grains i (0.06 gram)
Kalii (Natii) iodidi....................drams iii (12 grams)
Syr. sarsaparillæ comp............q.s. ad ounces iv (120 c.c.)
Sig.: 1 teaspoonful four times daily.

(*b*) *Pills.*—Pills for a long time were the basis of the mercury treatment of syphilis. Treatment with pills of mercury is the simplest form of treatment for the patient to carry out. For a patient who is traveling, pill treatment has a definite place, as an amount sufficient for a long period can be easily carried; he can take his pills unbeknown to any one. Pill treatment, however, is the least efficient form of administering mercury, and consequently mercury pills should be used only in the following situations: First, when a patient is traveling, or the circumstances are such that he can receive no other form of treatment; second, to fill in the interval between arsenical or other forms of mercurial treatments for short periods of time.

The following are a few of the better preparations of mercury for use in pills:

The most commonly used salt of mercury for pills is the *protoiodid,* which is given in doses of ⅛ to ¾ of a grain (.008 to .048 gram), three to five times daily. In the larger doses it frequently gives rise to abdominal pains, griping or diarrhea. To counteract these, a small amount of opium, about 1/10 of a grain (.006 gram), is placed in each pill.

One plan is to give the patient two boxes of pills, one containing opium and one without opium; the one with opium to be taken when the colic and diarrhea appear and the others to be taken at other times; or, we can give the patient the plain protoiodid pill and control the diarrhea and colic with paregoric.

Gastro-intestinal irritability, as manifested by abdominal pains, looseness of the bowels, diarrhea and, later, bloody stools, is rather common from the use of mercury pills. These symptoms should be combated in a prophylactic way by giving powdered opium in sufficient amount with the mercury to check them.

(*c*) *Capsules.*—The plain mercury with chalk powder can be mixed with a sufficient amount of sugar of milk, licorice roots or extract of gentian in the following capsule form:

℞

Hydrargyri cum creta..............	grain i	(0.065 gram)
Gentianæ extracti	grains iv	(0.26 gram)

M. Ft. capulæ No. I. Sig.: One four times daily.

The use of mercury with chalk powder has a decided advantage over manufactured pills and capsules, in that the mercury is certain to be absorbed. Pills, particularly if they are old, frequently harden so that they pass through the intestines entire.

(*d*) *Mercury Mixed with Iodids.*—Mixed treatment, namely, pills containing mercury and potassium or sodium iodid, can be used, but their usefulness is rather limited.

Mercury by inhalation and fumigation has been used, but these methods are not satisfactory except in institutions where the patients can be under complete and frequent observation, owing to the uncertainty as to the amount of mercury actually absorbed by the patient.

(2) ADMINISTERING MERCURY ENDERMICALLY, RUBBINGS OR SMEAR CURE.—Mercurial rubbings have been used for a long time in the treatment of syphilis. The preparation ordinarily used is the common mercurial ointment or blue ointment, of the United States Pharmacopeia, although preparations using metallic mercury and cacao butter are a trifle more cleanly. Preparations of calomel, prepared in a cacao butter base, are having an extended use, even though their therapeutic activity is less. They have the advantage, however, of being white and therefore very clean preparations. This is smeared upon the skin, an area of the skin as free from hair as possible being selected; definite hairy areas, such as the axillæ and pubes, should be avoided.

(*a*) *Preparation of the Skin for Inunction.*—The skin should be washed with warm water and soap immediately preceding the application of the salve. It should be thoroughly dried, then the salve applied and rubbed gently but firmly for from 10 to 20 minutes. The excess should not be wiped off, but should be left in place and allowed to soak into the undershirt. If it is necessary to remove the excess, we should use a larger amount of salve, smear it over a larger area of skin and rub longer, so as to compensate for the absorption that occurs from the impregnated undershirt.

The *average dose* of mercurial ointment, when used as an inunction for treating syphilis, is 1 dram, once daily. This, of course, should be increased or diminished if we have an unusually large or unusually small individual as a patient. If we have the patient at rest in an institution or a watering place, undergoing daily hot baths, we can give him much larger doses of the salve—up to 2 or even 3 drams daily.

The use of mercurial salve as an inunction is dirty and inconvenient in ordinary private practice, but this treatment has the great offset to its uncleanliness in the fact that its therapeutic value is very high.

(*b*) *Technic.*—A definite area of skin should be inuncted each night, according to the following schedule:

First Night: Inner surface of left arm.
Second Night: Inner surface of right arm.
Third Night: Adductor surface of left thigh.
Fourth Night: Adductor surface of right thigh.
Fifth Night: Lower left abdomen.
Sixth Night: Lower right abdomen.

The seventh night a bath should be taken and all the old salve cleaned off, and then treatment is begun again, using the same areas as before. Occasionally, the mercurial salve is irritating to the skin and a simple erythema or a pustular perifollicular rash may develop. If either of these skin lesions occurs, no more salve should be used upon the irritated areas until they are thoroughly well. If they recur upon subsequent application of the salve, the patient should not be subjected to further inunctions but we should change to some of the other methods of administering the drug. Treatment with rubbings should be continued in courses of from 20 to 40 days' duration, with a rest of from 2 to 4 weeks after each course.

(*c*) *Administration of Mercury by Pads of Cloth.*—The administration of mercury by the use of pads of cloth impregnated with metallic mercury and worn on the chest has had some vogue, and in certain types of cases it is a method of considerable value. It has the advantage of cleanliness and secrecy; the disadvantage of inaccuracy of dosage and consequent uncertainty as to its therapeutic effect. The pad is worn on the chest or back; the heat of the individual's body vaporizes the mercury and thus it is absorbed through the skin and by inhalation. Another method of using the mercury salve has been to place it on the feet, put on a stocking, and as the individual walks about as usual, every step of course rubs in some of the ointment.

In carrying out a course of rubbings, it is best to have the patient wear a light cotton undershirt next to the skin. This shirt will gradually become impregnated with the excess of the salve, but it should not be changed oftener than once a week, as some of the excess of the salve is absorbed when the shirt is continuously worn. This shirt also protects the outer clothing from being soiled.

When inunction treatments are given to a patient by a nurse or attendant, rubber gloves should be worn or the rubbing done with a glass pestle in such a manner that the hands of the attendant do not come in contact with the salve. If the bare hand is used the attendant may absorb as much mercury as the patient.

(3) INTRAMUSCULAR INJECTIONS OF MERCURY.—There are two types of mercurial preparations that are used for intramuscular injections: one is an insoluble salt, and the other a soluble salt. The frequency of injections, their local and systemic effects and the general course of treatment differ markedly from each other.

(*a*) *Injection of Insoluble Preparations.*—Insoluble preparations are given once weekly and have the advantage of introducing into the muscular tissues a relatively large quantity of mercury, which acts as a depot and is gradually but continuously absorbed into the blood and plasma, for a period of about a week, when the ordinary dose is administered. If the patient's absorption is poor, the dose may last longer, and if the absorption is relatively rapid it will last a much shorter period of time. If the injection is very irritating to the tissues, a fibrous wall may form about the mass of mercury; and because of this exudate relatively little absorption of the mercury will take place. All of these factors should be carefully considered and are very important in regard to each individual's treatment.

Dangers of Insoluble Injections.—The inconvenience and dangers of insoluble preparations can be summed up as follows: The patient may not absorb all of the mercury injected before the second injection is made; he may still be absorbing mercury from the first and second treatments when the third is administered; and in this way, absorbing mercury from multiple injections, and consequently getting more of the drug than he can tolerate, he becomes intoxicated—quite a serious condition, because the only way we can stop the absorption of mercury into his system is by a surgical removal of each of the injected areas.

Next, if these insoluble salts are injected into a vein, there is danger of embolism occurring. The pain produced by these injections is very variable; some of the patients complain bitterly of it, while others tolerate the injections very well. As a rule, it is rare to administer injections without having some of them cause considerable pain and marked infiltration. These infiltrations remain for a very long period of time as nodules, which may or may not be sensitive.

Specific Insoluble Preparations.—The most commonly used insoluble preparations are *gray oil* and the *salicylate of mercury.* The gray oil is 40 per cent. *metallic mercury,* rubbed up with *lanolin.* Strange as it may seem, the lanolin should not be resterilized, as it is sterile when taken fresh from the can in which it was purchased. The mixing of the lanolin and mercury should be done in sterile dishes and aseptic precautions observed; and the final product should be protected from bacterial contamination. If the lanolin is sterilized, some change takes place in it that renders it much more irritating to the tissues.

Dose.—The preparation is best used by filling a syringe, holding one cubic centimeter, with a graduated checked piston. The dose ordinarily given is from 1 to 4 turns of the thread of the piston, and represents 1 grain (0.065 gram) of mercury. The dose should be repeated once weekly to once in 10 days with from 10 to 20 injections in a series. The salicylate of mercury, best dissolved in goose oil, is also extensively used in doses of ½ to 1½ grains (0.03-0.10 gram). The general technic of injection and the frequency of administration is the same with the salicylate as with the gray oil.

Calomel is therapeutically the most active of the insoluble preparations of mercury, but unfortunately it is also the most irritating and painful. It is best prepared by washing the powder in alcohol and then mixing it with sweet almond oil, using a 5 to 10 per cent. mixture. This mixture should be vigorously shaken before being drawn into the syringe and the injection should be given at once before the calomel has an opportunity of settling out. The dose is from 5 to 10 centigrams (¾ to 1½ grains) of calomel at each injection, repeated once every 7 to 10 days.

Technic for Insoluble Preparations.—Intramuscular injections should be given, using needles sufficiently long to penetrate the subcutaneous fat and enter the muscular mass. The usual length is from 4 to 5 cm. As fine a needle as possible should be used, and after the needle is inserted one should wait a moment or two to see if blood comes out through the needle. If blood flows from the needle, it shows that the point of the needle is in a blood-vessel and the injection should not be made, for fear of embolism. If no blood flows, the syringe may be attached and the injection made.

Before the needle is withdrawn, a slight lateral or wiping motion should be made to try and wipe the salve from the end of the needle. This manipulation prevents the salve from being distributed along the tract of the needle as it is withdrawn. As soon as the needle is withdrawn, pressure should be made at the site of the puncture, and rotating, gentle massage movements carried out for a moment or two. Failure to carry out this step in technic probably accounts for many of the nodosities produced, and for some of the pain, in that the preparation, instead of being deposited in the muscle, is deposited in the fat underneath the skin.

The region best suited for injections of mercury, both soluble and insoluble, is the buttock; any portion of the buttock is suitable. It is best, however, to locate the sites of injection above or below the portion of the buttock subjected to pressure when sitting. These injections can be given into the muscles of the back, but it is not as practicable here as in the buttock. Insoluble injections should never be given in the arm.

The advantages of the intramuscular injection of the insoluble salts of mercury are: (1) great therapeutic efficiency; and (2) relative infrequency of administration. The disadvantages of this treatment are pain; but the greatest disadvantage is the development of multiple nodules, more or less painful, in the buttock.

(*b*) *Injection of Soluble Preparations.*—*Specific Soluble Preparations.*—The number of soluble preparations that have been used is very large, but the three most extensively used are the *oxycyanid*, the *bichlorid* and the *benzoate*. In a general way, the therapeutic activity of each of these preparations is practically the same.

Soluble versus Insoluble Preparations.—There is considerable discussion as to the superiority of soluble over insoluble preparations. They are, without doubt, inferior in therapeutic activity to insoluble mercurial salts, administered intravenously. The greatest handicap to the use of the soluble salts is the necessity for giving them often—daily, every other day, or, at least, twice weekly; they have the advantage, however, of having no cumulative action. Each injection is not so painful as an injection of insoluble preparations, but more injections are required. The benzoate is the least painful of any of the soluble salts.

Dose.—The following prescriptions are useful, to be used for intramuscular injection:

Benzoate of mercury	6 grams	(grains 92.6)
Salt	.75 gram	(grains 11.5)
Sterilized distilled water	100 c.c.	

This solution is injected in amounts of 1 c.c. every second day.

The bichlorid in 1 per cent. solution in sterile water is a very useful preparation when one wishes to inject a soluble salt, but it is quite painful.

Technic for Soluble Preparations.—In injecting soluble mercurial salts intramuscularly, the technic should be the same as when injecting insoluble salts, care being taken not to inject into or near a nerve, and care being taken that the salts are really injected into the muscular substance. Unless the patient has ready access to his physician, the soluble salts are not suitable for use in his particular case.

(4) INTRAVENOUS ADMINISTRATION OF MERCURY.—The intravenous administration of the soluble salts of mercury was first introduced by Baccelli. Intravenous injections of mercury were used in the pre-arsenic days, chiefly for cases of malignant syphilis and to control lesions that were involving or threatening to involve very important structures, as under these circumstances it is extremely important to check the disease at the earliest possible moment to prevent the destruction of important organs.

Specific Preparations.—The preparations used are *solutions* of *cyanid* and *bichlorid*. The writer prefers bichlorid solution, made in such a way that 5 c.c. of the solution in plain water contains 1/20 grain (0.003 gram) of mercury bichlorid, to be given every day, every other day, or at least twice weekly. Bichlorid of mercury solutions produce coagulation and precipitation of the albumins of the blood, but the thick, curdy albuminate of mercury formed in the syringe when the blood and the solution meet is immediately dissolved by the mass of serum in the blood-stream when injected into the general circulation. The cyanid of mercury, however, does not precipitate the albumin of the blood, and, consequently, is a little easier, technically, to inject; but in the writer's experience with it there has been more irritative phlebitis when using it than when using a bichlorid solution.

Advantages of Intravenous Injections.—The advantages of intravenous injections are: (*a*) complete absence of pain and (*b*) ease of administration. When a doctor is properly equipped to administer them, these treatments can be given very rapidly and easily. The absorption and elimination of the drug is rapid and certain, the mercury appearing in the urine at the end of one hour, and its maximum at the end of 3 to 6 hours. There is no chance of cumulative effects and we can administer these injections at as short or long an interval as we may elect. We avoid all gastric irritability, but intestinal irritability—particularly in the cecum and small bowel—may be quite severe if we slightly overdose the patient; however, this irritation is soon relieved by simply stopping the treatments for a day or so.

The therapeutic effect of the intravenous injections is extremely rapid and satisfactory and enormously superior to that of all the other methods of mercurialization. It can only be compared to the effect of calomel intramuscularly on tertiary lesions. However, the therapeutic effect of intravenous mercury is not quite as rapid as the effect of salvarsan. The chief and only drawback to intravenous injection of mercury is the technical ability of the doctor; if the injections are not truly intravenous we will have swelling and infiltration in the arm, accompanied by very severe pain.

Dose.—In giving the cyanid in 1 per cent. solution, the ordinary dose is 1 c.c. It is prudent, however, to commence with an injection of only ½ c.c., if there is any doubt as to the patient's tolerance of the drug. This should be repeated every day or second day for from twelve to fifteen days; then suspended for from a few days to a week; and then another course carried out. When one wishes to give intensive treatment to a patient who is tolerant, one may give him 1 centigram (1/6 of a grain) one day; 2 centigrams (⅓ of a grain) the next day; 1 centigram the third day; and 2 centigrams the fourth day. Thus, the dose can be regulated very accurately to the patient's tolerance of the drug and the therapeutic necessities of the case, increasing or diminishing as the need varies.

Technic for Intravenous Administration of Mercury.—The technic of the intravenous injections of mercury is extremely important and attention must be paid to every detail. First, the *syringe.* An all-glass syringe of from 5 to 10 c.c. capacity should be used, armed with a fine No. 23 needle, very sharp, and with as short a bevel as possible. The patient should either stand facing the operator, or lie on a table, the arm being uncovered up to the middle of the biceps and the forearm held in the left hand of the operator. A constrictor is placed around the arm, in the lower third, with just sufficient pressure to produce venous stasis, but not sufficient to stop the arterial flow. The constrictor consists of a piece of pure rubber tubing, which is pulled out away from the arm, then clamped with a strong clamp. The elasticity of the rubber draws the clamp down to the skin of the arm. In this way the skin of the arm is prevented from being caught in the grasp of the forceps. If the veins do not swell up immediately, one should feel for the patient's pulse; if the pulse is gone, it is an indication that the constrictor is applied too tightly. If the pulse is present, the patient should be asked to open and close the hand vigorously several times. When the veins have become distended, the operator should then select a suitable vein. If the veins are not prominent, the forearm and bend of the elbow should be palpated and the vein selected which feels the largest.

The operator then takes the syringe, which is filled with the mercury solution, and, armed with the needle in the right hand, makes the skin over the vein tense with the thumb of his left hand and notes carefully the exact direction of the vein. The needle is held in such a position that it follows exactly the course of the vein and almost parallels the skin surface of the arm. The needle, with the opening upward, is next inserted through the skin. The syringe is raised a trifle, forcing the needle downward through the wall of the vein. As soon as the needle pierces the wall of the vein, there is a sensation of lessened resistance, and blood appears in the syringe. This sensation is peculiar and can only be appreciated by feeling it.

If the needle is large and in the lumen of the vein, the blood immediately begins to flow back through the needle and into the syringe. If the needle is very fine (as it should be), one must allow a few seconds to elapse or even pull on the plunger a trifle before the blood appears. As the plunger of the syringe is withdrawn, there should be a very free flow of blood into the syringe, if the point of the needle is in the center of the lumen of the vein. If the flow of blood is not free and rapid, something is wrong: either the point of the needle is only partly in the lumen of the vein, or the needle has partly traversed the wall of the vein, or it has pierced a vein valve. Blood is then aspirated into the syringe, and by raising and lowering the patient's arm, this blood is thoroughly mixed with the mercury solution.

While these manipulations are being carried out, great care should be taken that the relations between the vein, the needle and the arm are maintained, so that the needle will not pierce the wall of the vein and allow the injection to infiltrate the tissues. When the blood comes in contact with the mercury solution, there is an immediate curd-like precipitate formed. This curdy mass can be injected and need cause no concern, as this albuminate of mercury is dissolved quickly in the excess of serum in the general circulation. The constrictor is then removed and the operator presses the plunger of the syringe, and so slowly injects the solution. If the technic has been proper, the fluid will flow steadily and easily. If a slip in technic occurs, or if one is in doubt if a slip has occurred, one should stop immediately, withdraw the needle and commence anew on the other arm. When the injection has been completed, the needle may be quickly withdrawn and the point of the puncture immediately pressed with a sterile piece of cotton or gauze, making particular pressure upon the vein just distal to the point of puncture. This should be accompanied by elevation of the patient's arm.

The *points to remember* in intravenous injections of mercury are:

First, is the needle in the vein? Second, has the needle, during any of the manipulations, slipped out of the lumen of the vein? If there is any doubt, the injection should be immediately stopped and the needle withdrawn. The points to watch particularly are *pain, local tumor* and *abnormal resistance to the progress of the plunger;* if any of these accidents occur, stop injecting at once and withdraw the needle.

As soon as the injection has been completed, the syringe and needle should be washed and water forced through the needle, sufficient to wash all blood out of its lumen. Unless these precautions are observed, the needle will be clogged with coagulated albumin when it is boiled for the next injection.

Really obese persons are not so hard to inject as the type of case that has lost some weight, or as elderly persons whose veins are unduly movable under the skin. In most people, there is a vein on the external aspect of the forearm that is relatively small, but markedly fixed in its position in the tissues; it can be readily located by palpation, and because of its immobility it is relatively easy to puncture. Another situation where the injection can be made is in the veins on the back of the hand; and particularly in obese persons are the veins on the anterior aspect of the wrist plainly visible and suitable for intravenous injection. Occasionally it may be necessary to give injections into the veins of the lower extremity. These should not be used unless absolutely necessary, as their wall is thicker, they are harder to puncture, and there is more danger of subsequent hemorrhage in the tissues when the patient arises and walks.

Dangers of Intravenous Injections.—The only accident of any importance in giving intravenous injections of mercury is the penetration of the fluid into the wall of the vein or into the tissues surrounding the vein. The danger of intraparietal injection is much increased by the use of a needle with a long point; there may be no sense of pain immediately and no marked local tumor, but usually when the patient returns the following day he will be found to have a sensitive, infiltrated chord immediately following the course of the vein. The injection of the mercury solutions outside of the vein gives rise to immediate pain and immediate local tumor. If either of these occurs, the injection should be stopped at once. Unless a relatively large amount of blood is aspirated into the syringe and mixed with the mercurial solution, chemical phlebitis may develop from the irritating action of the solution upon the vein lining itself. It is to obviate this accident that we aspirate the blood into the syringe and thoroughly mix it with the solution, thus changing the mercurial preparation to the non-caustic albuminate of mercury.

The only operative accident of importance is the failure to introduce all of the solution into the lumen of the vein. For some reason or other, the fluid is injected into the cellular tissue around the vein. This accident is much more likely to happen when needles with a long bevel are used. It frequently occurs that the point of the needle is in the lumen of the vein, and blood will be aspirated into the syringe when suction is applied; but the blood flow is not as free as it should be, since only part of the lumen of the needle is in the lumen of the vein; consequently, when one attempts to inject fluid, part of it goes into the vein lumen and part into the cellular tissue around the vein.

Injection into the cellular tissues about the vein can also occur when the needle is introduced at too great an angle to the axis of the vein and so pierces the deep wall of the vein. This occurrence is observed only if one keeps a sharp watch on the tissues at the point of injection and notes a small, deep tumefaction, and also if the patient simultaneously complains of pain.

As soon as one observes that the fluid has been injected outside of the vein, injection should be stopped at once and one should immediately try to aspirate as much of the injected fluid as possible. If the syringe is too full of the mercury solution to permit one to aspirate well, the syringe should be taken off and an empty syringe connected to the needle. In this way, with strong aspiration and gentle manipulation of the needle, one may be able to aspirate most of the irritating fluid.

In addition to aspiration, the part should be kept at rest and hot wet compresses applied, renewing them frequently. This accident in the hands of a careful operator, as a rule, is not serious—simply a little pain and a little irritation, with the development of a slight nodule at the site of the injection in a day or two; but if one is not familiar with the fact that perivenous injection of salvarsan solution and mercury solution will produce pain and that a normal intravenous injection is painless, one may continue injecting after the patient complains of pain. Under these circumstances the reaction may be very severe, involving the entire arm and ultimately producing more or less destruction of tissue and sloughing at the site of the injection. If any quantity of the solution is injected outside of the vein, the patient will have a swollen, red and exquisitely aching arm for from 2 to 6 weeks. This arm should be put at rest and hot applications applied to it as long as the swelling and the pain are present. *Morphin* is frequently necessary to relieve the pain.

After intravenous injections, there is frequently observed some subcutaneous ecchymosis. This very minor accident can be prevented by applying pressure with a small pledget of cotton or gauze to the point of puncture, immediately after the withdrawal of the needle, at the same time elevating the arm. The pressure of this pledget should bear upon the vein at the point of puncture and slightly distal to it.

Occasionally, in nervous and hypersensitive individuals, the prick of the needle causes them pain, which continues for several minutes. If there is any unusual complaint of pain, from the prick of the needle, it is wise to wait until this pain has disappeared so as not to confuse it with pain due to fluid injected outside of the vein.

Another complication following intravenous injections of mercury is a chemical phlebitis. This only occurs if the mercury solutions are injected very rapidly, without withdrawing and mixing a few cubic centimeters of blood with the mercury solution. The plain bichlorid solution is very irritant, but the albuminate solution formed by allowing the blood to combine with the bichlorid solution in the syringe is absolutely non-irritating locally.

Theoretically, intravenous injections should occasionally cause emboli. The writer has never had such a case and has been unable to find any such case described in the literature.

After-treatment of Intravenous Injections of Mercury.—Mercury injected into the veins is very rapidly absorbed—much more rapidly than with any other method of administration. This fact is one of the great advantages of the method; it is also the basis of the possibility of producing complications, namely, mercurial colitis or enteritis. This comes on several hours (rarely less than one hour) after the injection, beginning with sharp pains in the center of the abdomen, with a more or less abundant diarrhea which may become serous and ultimately bloody. These symptoms last one, two or three days and sometimes, because of bloody stools, may produce a moderate anemia. Treatment consists of applying **heat to the abdomen** in the form of hot-water bottles, or a heating pad, and the giving of **sufficient opium to check the peristalsis and relieve the pain.** The diet should be very bland.

This complication can be prevented by giving only small doses of mercury intravenously to any patient who complains of intestinal symptoms, to weak, anemic patients, or to any one giving a history of unusual susceptibility to mercurials. Likewise, no patient should be given a first or any subsequent injection of mercury who has recently eaten any acid in the form of fruits or vinegar. A patient with albuminuria should be treated very carefully by intravenous injections and, if these are employed, they should be given in very small doses, frequently repeated.

While every patient should have his mouth and teeth examined and, as a matter of routine, should clean his teeth regularly, it occasionally happens that a gingivitis develops or a stomatitis, either with or without some salivation. If any one of these conditions develops, one of two things should be done: either the dose of the mercurials should be decreased, or, better, the mercurial injections should be stopped and the salvarsan preparations given in small doses (say .15 to .3 gram, every second to third day) until the gingivitis or stomatitis—whichever it may be—has healed. Then, when one starts in to give mercurials again, they should be given in smaller doses and the patient should be watched carefully for the first sign of any complication. Should the complication develop, treatment should be stopped at once; none developing, it should be continued, and ultimately a normal dose may again be administered.

(5) Administration of Mercury by Rectum.—(*a*) *Suppositories.*—Administration of mercury in the form of suppositories was first brought out by Audery, of Toulouse. This form of mercurial treatment was first given to cases in which mercury by mouth or by the skin caused complications that necessitated cessation of the treatment. Rectal adminis-

tration of mercury is well tolerated by most patients locally, and there is a marked systemic and therapeutic effect from the mercury absorbed in this manner. Rarely is there irritation in the rectum, practically never any irritation in the stomach, and rarely trouble in the bowel. The indications for its use are the same as those for the use of mercury by any other method; it can be used as a substitute for mercury by mouth, by intramuscular or intravenous injections. It is given in a suppository containing ½ gram (7.716 grains) of metallic mercury, with a sufficient quantity of cacao-butter; these suppositories are given in doses of 1 or 2 daily, and are the therapeutic equivalent of rubbing or intravenous injection of mercury. The effect of the suppositories is particularly rapid and certain, especially as regards lesions around the anus, scrotum and in the throat. In urgent cases, this method is applicable and certain to mercurialize patients rapidly. As a rule, there is no local irritation of the rectum by the suppositories, but at times and after prolonged use they may cause some irritation of the rectal mucosa. If irritation is produced, suppositories should be discontinued and the mercury administered by some other route.

(*b*) *Inunctions.*—Mercury when used in the form of a salve and smeared or rubbed upon the skin is absorbed by volatilization and inhalation through the lung, or by direct absorption through the skin. The non-volatile salts are absorbed directly through the skin or mucous membrane, but their absorption is far slower than that of the volatile salts. The best preparation for an inunction treatment of syphilis is the old standard mercurial ointment of the United States Pharmacopeia. The cleaner ointments, made with calomel, absorb much slower than the regular mercurial ointment, but they are absorbed sufficiently so that they are useful when placed in the rectum.

No absolute preference should be given to any one of the methods of administering mercury, since there is no one remedy which suits every case. The choice of mercurial medication should be based on clinical indications relative to the peculiarities of the patient and the quality of the disease, rather than upon the therapeutic consideration. *The best method* is that tolerated by the patient and which has an active influence on the symptoms.

The rules adopted by Fournier and his followers are as follows:

The treatment is continued in a regular manner for 4 years, until neither syphilis nor any of its clinical lesions is manifest. Mercury represents the fundamental antisyphilitic. It is administered from 6 to 8 months the first year, 6 months during the second and third years and 4 months during the last year. During the course of treatment in the third and fourth year, potassium iodid is frequently used with it. About 1905, Fournier concluded that this treatment was not sufficiently long to prevent the appearance of general paralyses and of tabes, and he advised giving, after two years of rest, two more years of treatment—the seventh and eighth year.

PHYSIOLOGICAL ACTION OF MERCURY.—That mercury acts directly on the *Treponema pallidum* is quite probable, for the results obtained by using this drug as an antisyphilitic remedy are quite uniform, even when the symptoms vary considerably. Mercury is quite rapidly absorbed; the rate of absorption varying with the method used and the nature of the mercury salt, whether soluble or insoluble. The former is more readily absorbed. When mercury is injected in the form of bichlorid, it makes its appearance in the blood very early. Wilms was able to detect it in the blood taken from the ear of a rabbit 15 minutes after it was injected.

Any of the body tissues are capable of absorbing mercury, but mucous tissue or denuded surfaces absorb it most readily. After it is absorbed, the mercury circulates about in the body as a compound of mercury, the albuminate and sodium chlorid. It is generally distributed throughout the body, but it is especially stored up in the liver. Therapeutically, it has little direct action on any of the tissue, but improvement in the blood and nutritional state seem to follow its use in repeated small doses.

Mercury is excreted by the salivary glands, stomach, kidneys, skin, colon and rectum. It appears in the urine in 3 to 24 hours after injection and in the feces after 24 hours. After a subcutaneous injection more of the mercury is excreted in the sweat than in the urine. In the intestinal tract, the greater part of the mercury passes through the walls of the colon and the upper rectum and may cause irritation or even colitis. In the nursing mother, some of the mercury is eliminated in the milk.

The degree of tolerance for mercury varies with the individual and depends upon the rate of absorption and the ability of the body tissues to excrete it in amounts sufficient to prevent intoxication. This tolerance is just short of the toxic dose and there are symptoms which more or less indicate when the limit of tolerance has been reached and the patient has become mercurialized. The patient feels ill, has headaches, lassitude, muscular weakness and diarrhea, or occasionally he is constipated. Irritation of the gums is an early symptom and manifests itself by an increasing redness, swelling and a tenderness to pressure such as is produced when the jaws are forcibly brought together. Slight hemorrhages result from the least trauma. These symptoms are accompanied by an increase in the consistency and flow of the saliva. The breath has a characteristic fetor and the patient is conscious of a peculiar metallic taste in the mouth.

MERCURY INTOXICATION.—Once mercurial treatment has reached the point of the limit of tolerance, the stage of intoxication follows very rapidly, unless care is exercised and the amount of mercury administered is decreased, or treatment is discontinued for a time. The toxemia produced by mercury affects all the tissues of the body, but a few of them are especially affected. Mercury has a special destructive action on the epithelium of the convoluted tubules of the kidneys and often produces tubular nephritis. In case of an acute poisoning, this may be a violent exudative nephritis, while in a subacute or chronic case the nephritis is more likely to be diffuse and lead to destructive changes in the glomeruli, with an increase in the connective tissue. Anuria may occur; albumin, casts and red corpuscles are frequently found in the urine.

The mouth may be severely injured by mercury intoxication. The gums may become involved to the point of ulceration, the teeth may become loose, and even necrosis of parts of the mouth and jaws may result unless the mouth is given prompt and careful attention. Severe affections of the gastro-intestinal tract may occur as a result of the toxemia, such as severe gastritis or colitis.

Treatment of Mercurial Intoxication.—The success in the treatment of mercurial intoxication depends, first, upon the time that has elapsed between the intoxication and treatment; and, second, upon the nature of the treatment. In case the intoxication occurred by injection of a lethal dose of a mercury salt, egg albumen should be rapidly administered. This forms the insoluble albuminate, which should then be removed from the stomach by gastric lavage, and more egg albumen should be given. Fantus and Hyatt showed that the use of milk as an antidote was of no more value than the use of water, since it was the diluent action of each alone which was of value.

Various chemicals have been advocated as antidotes and have met with more or less favorable results. A mixture of sodium phosphite (10 parts), and of sodium acetate (6.6 parts), known as Carter's Solution, has produced fairly good results in treating mercury poisoning. Fantus and Hyatt showed that the use of sodium hypophosphite and hydrogen peroxid had a decided antidotal value when administered 5 minutes after the poisoning occurred. The hydrogen peroxid probably acts as a catalytic agent and hastens the action of the sodium hypophosphite. This solution, however, seems to be inferior to Carter's Solution in some ways.

Wilms has done considerable research on the treatment of mercury intoxication and concludes that the use of calcium sulphid is certainly of value in the treatment of rabbits poisoned with bichlorid of mercury. He found the use of calcium sulphid effective even when given 5¾ hours after the poison had been administered to rabbits. The preparation used by Wilms is an aqueous solution of calcium sulphid in a strength of 1 grain of the salt to 1 ounce of distilled water. The solution is prepared by dissolving the calcium sulphid in boiling water and filtering it while hot.

In advanced cases of poisoning with bichlorid of mercury, the intravenous method of administering the calcium sulphid is the most effective method, being sure to use 1 grain of calcium sulphid to each grain of mercury taken. In case the intravenous method is not practicable, the antidote may be administered by mouth. It should then be given until all the symptoms of intoxication have disappeared. Dr. Ireton records a case of recovery where the calcium sulphid was administered to the patient 12 hours after the ingestion of the poison. This appears to be the simplest, most certain and quickest method of combating mercurial intoxication.

Only freshly prepared calcium sulphid should be used, since a deteriorated solution leads to severe convulsions, due to the action of the calcium on the spinal cord; besides, the fatal poison, hydrogen sulphid, may form in a deteriorated solution.

Arsenic.—Arsenic has been employed for a long time in the treatment of syphilis; probably first as Donovan's Solution in 1839, but in this early period it was used as an adjuvant to potassium iodid and to mercury. Most men considered it simply as an energizer of the mercury and iodid, and not as having any particular value in itself. It was prescribed particularly in cases showing a marked anemia. Next, arsenic was used as a principal antisyphilitic remedy in the form of atoxyl. This drug has a very short clinical life because of the serious complications produced by it upon the optic nerves. In 1909, two arsenical preparations were brought out, one by Mounyrat in France, which was marketed under the name of *Hectine* and had a chemical name of "benzo-sulphone-para-aminophenylarsenate of soda." It was also used in combination with mercury in a preparation known as *Hectargyre.* The second preparation, and the one that proved by far the better, was the dichlorhydrate of dioxydiamido-arsenobenzol, and known under the trade name of *Salvarsan,* or the common name of "606." It is also known under the chemical name of arsenobenzol.

ARSENOBENZOL (*Salvarsan*).—Arsenobenzol is a yellow powder, impalpable to the touch and with an astringent acid taste, giving off an odor somewhat resembling onions or garlic. It is unstable, and is readily oxidized to a brownish-blackish powder on contact with the air. It is marketed in sealed glass ampules, from which the oxygen is excluded. When dissolved in water, the salvarsan forms a clear yellow, slightly acid solution. This acid solution must be neutralized before the drug is suitable for clinical use. After neutralization, the drug can be administered either intramuscularly or intravenously, but preferably intravenously.

NOVARSENOBENZOL.—Arsenobenzol has been to a large extent displaced by a preparation known as Novarsenobenzol, or, chemically, "dioxydiamido-arsenobenzolmonomethylene sulphoxylate of soda," or "914." Novarsenobenzol is a yellow powder, which dissolves very rapidly in water at ordinary room temperature, giving a limpid yellow-colored solution of neutral reaction and suitable for direct injection into the veins. Novarsenobenzol is altered rapidly on contact with the air. It is marketed in sealed ampules, from which the oxygen has been excluded. It is extremely important that it be mixed fresh for each patient and no old solution used. If there is any brownish color to the powder, it should be discarded, or if, after the solution is made, it is not of a bright yellow color, the solution should not be employed. Another point in the use of novarsenobenzol is that it should be *dissolved only in water,* not in salt water, and *only in cold water.*

Kind of Water to Use.—Many of the accidents that have occurred following the use of novarsenobenzol have been attributed to the water that was used in making the solutions. The water has been accused of causing severe reactions and severe toxic phenomena from two standpoints: the chemical and the microbic impurities. Alkaline waters, or waters containing silicates, or lead salts, should not be used. Ordinary water that contains none or relatively little of alkaline salts can be used, but it is best to use only distilled water—better double distilled—and, best of all, distilled the second time on the same day on which it is used.

When arsenobenzol was first introduced by Ehrlich, he advised that 50 c.c. of water be used to each decigram of the drug. Revaut showed that this amount was much larger than was necessary, and this fact simplified the technic very greatly. He demonstrated that a solution of arsenobenzol containing 45 centigrams (6.75 grains) to 10 c.c. of water was isotonic with the blood-serum, and, consequently, he advised that solutions of novarsenobenzol for intravenous use be made in the following manner:

.15 gram	3.33 c.c. water
.3 gram	6.6 c.c. water
.45 gram	10.00 c.c. water
.6 gram	13.3 c.c. water
.75 gram	16.6 c.c. water
.9 gram	20.00 c.c. water

Revaut showed, further, that the quantity of water could be still further diminished with no particular trouble, and, as a matter of fact, with great benefit, as it is less trouble to administer the smaller amount, and the likelihood of reaction upon the part of the patient diminishes in direct proportion with the amount of water injected. This concentration may be carried down to the point of dissolving .9 gram in 2 c.c. of water. This concentrated solution does not alter the blood, but it is very irritating to the tissues, if a drop or two is injected outside of the vein. In using these concentrated solutions, they should be injected very much more slowly than the more dilute ones. If it is impossible to obtain distilled water, an ordinary well water or rain water may be used, after boiling it to precipitate the lime salts, letting it stand to allow them to settle out, and using the water from the top of the vessel obtained by decantation. The use of the concentrated solutions has markedly diminished the number and severity of the reactions following the administration of novarsenobenzol.

Novarsenobenzol can also be used as an *intramuscular injection,* but it should be used in this manner only in exceptional cases, because the pain and nodosities caused by it are frequently rather annoying. Likewise, the therapeutic effect from intramuscular injections is not as rapid nor as complete as those following intravenous injections.

Effect of Novarsenobenzol on Syphilitic Lesions.—The action of novarsenobenzol on active syphilitic chancres is very rapid. The first day following the injection the chancre becomes less red and has a much paler appearance; its edges are less hard and less sharply defined. Induration has diminished somewhat and its appearance is more that of a simple ulceration than of a true hard chancre. In from 6 to 12 days it is completely healed. Simultaneously with these changes in the chancre, the regional lymphatic glands cease to enlarge, become less hard, and in a few days they have retrogressed to their normal size. The secondary lesions are likewise markedly affected by intravenous injections of novarsenobenzol. Mucous plaques in the mouth and around the anus, vagina or rectum change from progressive spreading lesions to retrogressive healing ones over night, and are usually healed in from four to six days. The hypertrophied plaques, or condylomata lata, are rapidly flattened out, and in from 8 to 12 days they have completely lost their papillomatous appearance and have disappeared practically completely. The cutaneous lesions likewise disappear rapidly after the intravenous injection of novarsenobenzol.

At first, within a few hours after the injection, these lesions become congested, enlarge somewhat, and in cases where there were no cutaneous lesions before, they may appear. This congestive phenomenon of the secondary lesions of the skin is known under the name of the Herxheimer reaction. This congestive condition lasts a day or two and then the lesions begin to fade out and rapidly disappear, the roseola disappearing in from 5 to 8 days. The muscular papular syphilid disappears in from 6 to 10 or 11 days. The small papular syphilids are most resistant to the treatment and many times they will not disappear in from 2 to 4 weeks. The syphilitic lesions of the late papular and gummatous type heal very quickly and cicatrize as fast as the epithelium can proliferate, and so cover the raw surface.

The beneficent action of novarsenobenzol upon syphilitic lesions is not confined to aiding the cutaneous lesions to cicatrize. Its action upon the visceral lesions of syphilis are just as rapid and effective in causing their disappearance as it is upon the cutaneous lesions. The syphilitic headaches of the secondary stage are practically always very quickly relieved by novarsenobenzol. The pains in the bones are likewise rapidly cleared, as are also the severe destructive lesions in the central nervous system. Iritis and choroiditis are quickly checked by the use of novarsenobenzol. The iris rapidly recovers its motility and resumes its normal color within a few days. The general health of the patient rapidly improves after the first injection; the syphilitic fever subsides; the anemia disappears; the general achiness in the muscles goes away; the color returns to the lips and conjunctivæ; and many patients state that they feel better than they have felt for a long time. The appetite returns and they eat well.

In the type of case with severe mouth lesions that have been treated unsuccessfully with mercurial preparations, the novarsenobenzol causes a rapid healing of the mouth lesions, together with a disappearance of the mercurial gingivitis and stopping of the flow of saliva that has been produced by the administration of mercury. Occasionally, we find an individual who does not tolerate the novarsenobenzol well, but in the majority of syphilitic cases of the first and second stage of syphilis, the general health of the patient is improved much more rapidly, and the improvement progresses to a point that is never attained by mercurial treatment, patients frequently gaining 5 to 10 pounds, and, once in a while, 20 to 24 pounds in weight, following the administration of 1, 2 or 3 injections of novarsenobenzol.

Therefore, we see that the influence of novarsenobenzol is peculiarly rapid and energetic upon the active manifestations of both early and late syphilis. But has it a real curative action? The original idea of Erhlich, that with salvarsan one should be able to produce a complete sterilization of the body, is known now to be fallacious. Can this sterilization be obtained by increasing the number of doses or by increasing the size of the doses? Opinion on this point is very much divided, some thinking that complete radical cures can be obtained and others stating that such a result cannot occur. One point, however, is established, and that is, if we are going to obtain an immediate sterilization of the syphilitic by novarsenobenzol, the drug must be administered early during the period of the chancre. When the drug is administered later than this, the number of cases immediately sterilized or radically cured decreases rapidly.

When we remember that salvarsan, as a therapeutic agent, is only 9 years old, we must reserve our judgment as to its ultimate effect upon syphilis. We know, however, that in the early cases lesions are healed and the Wassermann becomes and remains negative for many months, up to several years.

Another argument in favor of salvarsan for the cure of early syphilis—and one that should be given great weight—is the fact that under mercurial treatments it was very rare to find an individual who, having once had a definite chancre, would acquire another one. Since the advent of salvarsan, these cases of so-called "double infection" have become quite common. Consequently, we conclude that the original syphilis was cured and that the individual had acquired a new infection.

It is remarkable that with the treatment of syphilis by arsenobenzol in the chancre stage, the characteristic lesions of the secondary stage are ordinarily absent, but the tertiary lesions often appear very much earlier in a syphilis treated by salvarsan than in one not treated at all, or one treated by mercury. It seems that the arsenic retards or cures the secondary lesions, but hastens the development of the later manifestations of syphilis. On the other hand, many observers report cases treated with several doses of novarsenobenzol in the early period of the chancre in which patients have remained free from syphilitic lesions, and the Wassermann remained negative for two or three years. Therefore, we may conclude that the arsenobenzol will definitely cure syphilis when it is applied early in the initial period of the disease. Later on, the cures are not so definite and are much fewer in number.

Dose of Novarsenobenzol.—Ehrlich stated that the maximum dose of salvarsan should be one centigram per kilogram of body weight, and this dose ought never to be surpassed. Therefore, as the toxicity of novarsenobenzol is at least half again as great as that of salvarsan, the maximum dose of novarsenobenzol should be 1½ centigrams per kilogram of body weight. The majority of syphilographers think that these doses are much too large, and especially are they much too large for the first injection. All admit that the first injections ought always to be smaller than the later ones, and particularly is this true of the early cases in the secondary stage, either just before or just after the secondary rashes and mouth lesions have appeared.

The arsenobenzol kills so many of the large number of *Treponemata pallida* in the body at this stage of the disease that the emunctories are overwhelmed with the toxic material from the dead *Treponemata pallida.* Therefore, the first dose should be small, beginning with 3/10 gram of novarsenobenzol and increasing .15 each injection. Others state that we should start at .6 gram and increase .15 with each injection up to .9 gram. In the real early chancre stage and in the very late secondary and tertiary stages of syphilis, the dosage is not of so much importance, as there are at these times relatively few *Treponemata pallida* in exposed positions in these patients' bodies, and, consequently, we have only the toxicity of the drug to consider and not the uncertain amount of toxins that are liberated from the dead *Treponemata pallida* by the spirocheticidal action of the drug.

As a general rule, it is safe to give, as a primary dose, .45 to .6 gram to men of this class, and .3 to .45 gram to women. For anemic, nervous, emotional, albuminuric and arteriosclerotic individuals, the dose should be about .3 gram as an initial dose. If the first arsenobenzol injection is followed by a severe reaction, or any complications, we should be very cautious in administering the second dose, or, perhaps better, give the patient a carefully supervised mercurial course before giving salvarsan again. Many authors counsel that we should give as many as 10 or 12 doses of .45 to .6 gram salvarsan to a patient; some even advise more. In the writer's experience as much benefit is obtained from 3 or 4 injections as from a larger number. After the last salvarsan injection has been given, treatment may be continued by a mercurial course.

It is necessary to allow the body time to eliminate the drug and the toxins of the *Treponemata pallida* killed by the drug before giving a second dose. If we are using the standard average dose, the interval should be at least 5 days; better, 7. If we are using a very small dose, it is probably advantageous to give these at intervals of 3 to 4 days, but not more than 3 consecutive doses should be given within this short interval.

Clinical Course Following Injections of Concentrated Novarsenobenzol Solution.—The clinical course of patients who have received treatments of concentrated solution of novarsenobenzol is generally very simple. If regular three- or four-hour temperatures are taken, we will frequently find an elevation of temperature, which begins about 8 hours after the injection. This temperature is much less intense following the concentrated injections than following the non-concentrated ones. It is more intense after the first injection than after the subsequent ones; it is not marked among the patients who have numerous lesions containing a large number of *Treponemata pallida.* The temperature rarely goes to 104° F. (40° C.), ordinarily not going beyond 99.5° to 100° F. (37.5° to 37.8° C.). The late fever comes on the next day or second day following the injection, rarely going beyond 99.5° to 103° F. (37.5° to 39.4° C.), and passing away in about 24 hours. The fever is due to the toxins from the killed organisms.

Occasionally, and most frequently after the third injection, we have a lowering of the temperature below 98.6° F. (37° C.), coming on several hours after the injection and lasting for some hours. The fever in most of the patients is not accompanied by any other sign and ordinarily passes unobserved unless regular temperatures are taken. In others, it is accompanied by headache, by chills, nausea and vomiting. These phenomena are more frequently after the first injection than after the subsequent ones. A serous diarrhea, rarely abundant, but sometimes bloody, frequently appears in from 10 to 20 hours after the injection. Rarely, we may have a generalized scarlatiniform eruption and very rarely an urticarial rash, coming on very soon after the injection.

Precautions Following Novarsenobenzol Injections.—When novarsenobenzol is used in concentrated solutions, practically the only condition that develops, subsequent to the injections, is a slight temperature, of which the patient is not aware and which passes without his knowledge. Any of the technical accidents with mercury described under Dangers of Intravenous Injections (p. 395) may occur with novarsenobenzol, and they should be treated in a similar manner. It is best for the patient not to eat for 3 hours immediately preceding the injection; after it, only moderately, and he should first return to his normal diet on the following day. After the injections he should go to bed, or, at least, lie down in his room on a couch for the rest of the day. When injections are given in the office, the patient should return to his home as soon as possible, and carefully avoid physical exertion wherever possible.

GRAVE ACCIDENTS FOLLOWING ARSENOBENZOL AND NOVARSENOBENZOL TREATMENTS.—The conditions favoring the development of these accidents are multiple. Their pathogenesis is complex and their interpretation has caused much discussion. These accidents can be divided into two groups: (*a*) technical faults; and (*b*) true toxic effects.

(*a*) *Technical Faults.*—The technical faults are, first, the use of too large doses. Second, the use of too large doses in proportion to the visceral lesions of the patients. Patients afflicted with serious lesions of the heart, liver, kidneys or aorta, should be given smaller doses than relatively normal individuals. Third, the use of solutions that are old or improperly prepared, as incomplete or non-neutralization of the acid salvarsan solution, will produce very severe symptoms, and even death.

(*b*) *True Toxic Effects.*—The types of lesions due to the inherent toxicity of the drug itself are, first, acute encephalitis. This appears usually after the first or second injection, rarely later, coming on within the first three days subsequent to the injection. It is characterized by an extremely violent headache, high temperature, congestion of the face, delirium, coma, repeated epileptiform convulsions and vomiting, and ends generally in the death of the patient in a relatively few hours. Postmortem there is found intense hyperemia, hemorrhage in the brain substance and marked acute degenerative changes in the kidneys. This is the case in most of the deaths following the injection of arsenobenzol or novarsenobenzol. This type of lesions is always found in subjects apparently healthy, young, vigorous adults, with no visceral lesions whatsoever. This accident occurs after the first injection, but most often after the second injection. It should be guarded against in individuals who show a marked fever, facial congestion and the phenomena described by Milian, under the name of "nitroid crises"; also, among patients who show a measliform or scarlatiniform rash. Patients showing these phenomena after the first injection should be given a very small dose at the second injection, or the second injection should be omitted entirely and a mercurial course substituted.

(*c*) *The Neurorecidives.*—Under the name "neurorecidives" have been described isolated paralyses of the cranial nerves. These paralyses appear some weeks after the salvarsan injection, accompanied with intense headche, diffuse or one-sided pains in the neck, in the back or on the limbs. They appear, according to the statistics of Benario, in about the following percentage:

Auditory nerve	44.5 per cent.
Optic nerve	30.2 per cent.
Oculomotor nerve	7.4 per cent.
Facial nerve	7 per cent.

Involvement of the auditory nerve produces tinnitus and deafness, which may be unilateral or bilateral. Deafness is often complete and may be accompanied by marked vertigo and, rarely, by vomiting. The lesion of the optic nerve produces an optic neuritis, a neuroretinitis, or a retinitis with or without much functional disturbance, but blindness may result. When the oculomotor or facial nerves are involved, characteristic paralyses occur. Several of the cranial nerves may be simultaneously involved and produce a clinical syndrome which, because of the existence of lesions of the spinal nerves, is very complex. Lumbar puncture in these cases shows a marked lymphocytosis of the spinal fluid. After a variable time, most of these lesions heal, the most persistent being the auditory and ocular cases.

The explanation of these lesions is usually that of a basilar meningitis. At first, however, they were attributed to the toxic action of the arsenic, but these critics forgot the fact that these lesions appeared in the syphilitic subject before the syphilis was ever treated with arsenobenzol, and they never appear in patients afflicted with other diseases and treated by arsenobenzol.

Revaut has often shown that syphilis frequently produces meningeal lesions which remain latent, except as manifested by changes in the character of the spinal fluid. The arsenobenzol affects this latent meningitis the same as it affects the cutaneous lesions of syphilis, by producing a temporary congestion and swelling. This congestion and swelling, being confined by the bony walls of the skull, compresses these nerves to such an extent as to produce a temporary paralysis. These neurorecidives rarely occur in patients treated by a preliminary course of mercury.

Icterus is observed, following arsenobenzol injections, and it appears under several forms: one, a rapidly developing icterus and which disappears as rapidly—undoubtedly a true toxic phenomena. Icterus also appears in the clinical form of an acute yellow atrophy of the liver. *Albuminuria* and *intestinal irritation* occasionally develop, following arsenobenzol injections. They are cured rapidly by stopping the injections.

Acute rashes of the measliform and scarlatiniform type are rather frequent after the injection of arsenobenzol. They usually come on toward the end of the second day and are of considerable importance, as they signify severe intoxication and frequently are the forerunners of serious trouble.

Generalized exfoliative dermatitis is caused by arsenobenzol, and when it occurs is a contra-indication to any further treatment with the drug.

The pathology of most of these accidents is the same pathology as we see expressed upon the skin in the reaction of Herxheimer, and these phenomena almost always occur in tissues already invaded by the *Treponemata pallida.* These phenomena are much less frequent following novarsenobenzol injections than following arsenobenzol injections. However, on the whole, these accidents are relatively rare and should not cause one to discard novarsenobenzol from his therapeutic armamentarium.

When Ehrlich first gave salvarsan to the world he announced that it was capable of producing complete sterilization. Many thought that because of this statement mercury was superseded and had no further place in the treatment of syphilis. Before long Ehrlich's dictum was proven to be false and, as our experience with arsenobenzol becomes greater and greater, we now know that mercury not only is not superseded by salvarsan, but that it has as important a place to-day in the treatment of syphilis as it ever had. Cases treated with salvarsan alone' have a tendency to relapse much more frequently than cases treated with mercury alone, or with salvarsan and mercury.

Association of Mercury and Salvarsan.—Most syphilographers today advise the treatment of the early chancre and secondary lesions of syphilis with salvarsan. After these treatments have been given, the ground gained should be held by the methodic, persistent administration of mercury in the same manner as it had been used for so many years before the discovery of salvarsan. Mercury also has another place in the treatment of syphilis with salvarsan; namely, in early cases, where the individual is infected with enormous numbers of *Treponemata pallida.* In these cases a preliminary course of mercury destroys most of these organisms and therefore renders it safe to administer salvarsan subsequent to the mercurial course. In the routine treatment of syphilis, mercury can be given simultaneously or alternately with salvarsan, always bearing in mind that we are treating a patient who is a human being, as well as treating a disease; in other words, watching the patient's clinical condition closely for the development of toxic symptoms from the drugs administered or from the involvement of the viscera—particularly the kidney—by the disease. If for any reason his general clinical condition is not good, we should immediately ascertain if this lowered physical state is due to the disease; if so, the treatment should be increased. If his lowered physical state is due to the toxicity of the drug, it should immediately be lessened or the treatment stopped.

Plan of the Treatment of Syphilis

A. Primary Stage.—Having given the different methods of the treatment of syphilis, together with their advantages, disadvantages and dangers, we will now formulate a definite treatment plan, suitable for the average routine case. This plan can be modified to meet any complication or unusual conditions present in any particular patient. *Time* is the essence of the treatment of syphilis. An **early diagnosis** is many times more valuable to the patient than a late one; consequently, all **suspicious sores should be examined at once** and, if *Treponemata pallida* are found, treatment instituted immediately. Syphilis presenting itself in the period of the chancre should be given treatment with the briefest possible delay, with injections of novarsenobenzol.

In the *first two weeks of the chancre,* it is not necessary to precede the **novarsenobenzol injections** with any **mercurial injections**; in the *later weeks of the chancre*—and particularly if the patient has much adenopathy or is complaining of pains in his bones, joints or muscles—it is best to give him two or three **inunctions,** or two or three **intravenous injections of mercury.** These mercurial treatments should be followed by an **intravenous injection** of .45 to .6 gram **novarsenobenzol,** for a man of ordinary weight. Beginning the second or third day subsequent to this injection, he should be given an **inunction or an intravenous injection of mercury** each day for 3 days, then 8 days subsequent to his first injection of novarsenobenzol he should have a second intravenous injection of .6 to .9 gram novarsenobenzol. If the accompanying adenopathy has diminished markedly and if the chancre has almost or completely healed, it is not absolutely necessary to give any further injections of novarsenobenzol, but simply continue with the mercury treatment.

If marked changes in the syphilitic lesions have not taken place, 8 days after the second novarsenobenzol injection the patient should be given a third, there being always administered in the interval between the arsenic injections either an inunction of 1 dram of unguentum hydrargyri or an intravenous injection of 1/30 to 1/15 grain (0.002 to 0.004 gram) of mercury bichlorid every day or every second day. It is best not to give any mercury treatment the first day following the salvarsan injection, and frequently it is best to give none until the third day following the novarsenobenzol injections, if there has been much of a reaction.

Local treatment of the chancre consists of simply keeping it washed with boiled water—thus keeping it free from crusts and scabs—and, if desired, applications of mercury ointment once or twice daily. **Powders** should not be applied to the chancre, and **cauterization** should not be employed unless it is done very thoroughly and in such a manner as to completely destroy all of the infiltrated tissue. Some syphilographers are of the opinion that the **removal of the chancre,** or its **complete destruction by cautery**—when it is not so situated that it can be removed surgically—is of value to the patient, in that it removes all of the dense infiltrated tissues which serve to protect the *Treponemata pallida* from the action of the salvarsan circulating through the blood.

The **Wassermann reaction** should now be made, and in the average case it should be negative. If, however, the Wassermann is positive, another course of 2, 3 or 4 salvarsan injections with intervening injections of mercury should be carried out. If the Wassermann reaction is negative, the patient should be carried along on the ordinary mercurial course, as described on page 413.

B. Treatment in the Secondary Stage.—In this period, the treatment is practically identical with the treatment in the period of the chancre. The chief difference is that patients in the active secondary stage of syphilis with numerous cutaneous and mouth lesions have an enormous number of *Treponemata pallida* in their bodies. If most of these are killed at once by an **intravenous injection of salvarsan,** we are liable to have a very severe reaction and even a fatality. Hence, syphilitic patients at this stage of the disease should be treated first by 2 to 4 **inunctions or intravenous injections of mercury before the novarsenobenzol is administered.** Then, at eight-day intervals, 3 to 4 **injections of novarsenobenzol** should be given, beginning at .45 to .6 gram, and running up to .75 to .9 gram, with interspaced, daily or every second day, **intravenous injections or inunction of mercury.**

Local lesions in the mouth and ulcerative lesions around the anus, perineum and scrotum should be washed with **Labarraque's solution,** in the strength of 2 or 3 tablespoonfuls to the quart of water, several times daily. *Condylomata* should be carefully cauterized every second or third day with **acid nitrate of mercury,** or with a **silver nitrate stick.** Similarly, the ulcerative lesions on the lips, tongue, throat and cheeks should be touched with the same solution.

Secondary Lesions on the Skin.—When the secondary lesions on the skin manifest a tendency to ulcerate, the number of **injections of arsenobenzol** should be increased to 5 or 6, and, at the same time, attention being given to the patient's **general hygiene,** giving him **tonics** to build him up as much as possible. The following forms of secondary lesions on the skin are peculiarly resistant to arsenobenzol treatments: small papular syphilid, palmar psoriasis and the pustular syphilid.

It is necessary, when confronted by any of these lesions, to **repeat**

the injections of novarsenobenzol and to augment their action by giving **intravenous injections of mercury** with them; or, if they are very resistant, to give 1 or 2 **intramuscular injections of calomel.** It is also of advantage to give, with them, **baths of sulphur water,** which can be made artificially by the addition of a small amount of Vlemnickx's solution (solution liquor calcis sulphuratæ, N.F.) to the water in the bathtub.

Certain *visceral manifestations* need special medication and certain others need modification of the preceding methods.

Syphilitic Headache.—Syphilitic headache, if it does not yield to the above-described routine treatment, should be treated with one or two doses (grains 15-30 [grams 1-2]) of **potassium iodid** daily, by mouth. Also, if the headache is at all persistent, a **lumbar puncture** should be performed to relieve the increased intraspinal pressure, if present, and to ascertain if there is a true syphilitic involvement of the basilar meninges of the brain, which will be manifested by an increase in the lymphocytes in the spinal fluid. If this increase is found, a much more **prolonged treatment with novarsenobenzol** should be instituted and the advisability of giving some form of **intraspinal treatment** should be considered.

Facial Paralysis.—Facial paralysis, coming on in the secondary period, shows that there is a basilar meningitis present, and thus is a warning toward the necessity of being very **energetic and persistent** in our **treatment.** If the paralysis develops before any arsenical treatment has been given, one or two **injections of arsenobenzol** of .45 to .6 gram had best be given at once. If the facial paralysis comes on subsequent to arsenobenzol injection, it is best not to repeat the arsenic injections, but to treat him with **inunctions or intravenous and intraspinal injections of mercury.**

Syphilitic Hemiplegia and Frank Meningitis.—These conditions should be treated in the same manner, always remembering that salvarsan in medium to large doses produces a temporary congestion in syphilitic lesions. This congestion occurring in syphilitic lesions of the central nervous system may be a very serious matter. Therefore, **salvarsan** should be given in small doses (.15 to .3 gram), frequently repeated, every second day for 2 or 3 doses; then **intravenous injections of mercury bichlorid** (1/20 grain) every day or every second day should be given.

Iritis.—Iritis is quite a frequent complication of the secondary period of syphilis, and should be treated energetically both with **arsenobenzol injections and mercurial injections.** We should give from 4 to 6 injections of **novarsenobenzol,** beginning with .45-.6 gram and increasing up to .75 or even .9 gram in a large patient. At the same time, **mercury** should be administered in the form of inunctions, intravenous injections or intramuscular injections of gray oil, in suitable doses and at suitable intervals. Iritis cases should never be treated by the syphilographer alone; he should always have the patient consult an ophthalmologist. If no ophthalmologist is available, **atropin** in 1 per cent. solution should be placed in the patient's eye in sufficient amount to thoroughly dilate the pupil, and this dilatation should be maintained until the ciliary injection has disappeared and the iris has resumed its normal color. Four or five drops of the following prescription, placed in the eye twice daily, is usually sufficient for this purpose:

Atropin sulphate	0.1 gram (1.5 grains)
Distilled water	10.00 c.c.

Icterus.—Icterus in the secondary period of syphilis should be treated by **mercury alone,** either in the form of intravenous injections, intramuscular injections or inunctions—preferably by intravenous injections, as these are easiest controlled—giving small doses (1/40 to 1/30 grain), frequently repeated, and watching their effects very carefully. There is a tendency in this type of case to have *intestinal hemorrhages, due to the jaundice.* Mercury has an irritative effect on the intestinal mucosa also; hence, the need for small doses frequently repeated and careful observation. If, for any reason, **intravenous injections of mercury** cannot be given, recourse should be had to **intramuscular injections of the benzoate or bichlorid of mercury.** It is probably best not to give any **arsenic** in these cases; at least, until the icterus has disappeared and the liver returns to its normal size, because of the known marked toxic effect of the arsenic on the liver cell. Syphilitics with icterus in the secondary stage of syphilis should be watched very closely clinically.

Syphilitic Nephritis.—Syphilitic nephritis, in the secondary stage, showing albumen and blood in the urine, should be treated with the greatest of caution and should be very carefully observed clinically. As the **intravenous injections** are followed by very rapid elimination **of mercury** by the kidneys, it is dangerous to give them in any but small doses to this type of patient. It is best to give the **bichlorid or benzoate intramuscularly,** commencing with doses of .003 gram (1/20 grain), and gradually increasing up to .01 gram (1/6 grain), if the albuminuria does not increase. If the albuminuria diminishes during the mercury treatment, then one may commence to use **novarsenobenzol** in doses of .15 to .3 gram as a maximum. The patient should always be **in bed** during treatment and his **urine** should be **carefully observed**; and, further, he should be on a treatment and diet suitable for an individual suffering from acute nephritis.

Syphilitic Lesions of the Muscles and Bones.—Syphilitic lesions of the muscles and bones—and particularly the bone pains—are rarely persistent enough or severe enough to demand special treatment. However, if the pains are quite severe, the regular **routine arsenic and mercurial treatment** should be carried out, as outlined, and, in addition, from 1 to 3 grams of **iodid of potassium** should be given every day. If the pains are quite severe, **opium, bromids or chloral hydrate** should be given in sufficient amounts to at least mitigate the pain to the point of tolerance.

C. Subsequent Treatment.—The treatment as previously outlined is sufficient to free the patient from all active syphilitic lesions and to restore him to apparent health. It is necessary, however, to **follow this treatment by medication,** carried on for several years. If the patient is so situated that he can see his physician only rarely, he should be given some form of **mercury pill or capsule,** to be taken by mouth, such as the following:

℞

Mercury with chalk.....	grains i to ii	(0.065 to 0.13 gram)
Extract of gentian......	grains v	(0.324 gram)

Sig.: Four of these pills to be taken daily.

If he can report to his doctor in two months after the preliminary treatments, a **Wassermann test** should be given, also 2 to 3 injections of **novarsenobenzol** in doses of .6 gram (9 grains) at 8-day intervals. This should be followed by **another course of mercury pills, or capsules,** when he should report to his doctor in another two months, and if the Wassermann is negative he should have another injection of novarsenobenzol, followed by the mercury pills. If his Wassermann is positive, he should have a course of from 2 to 6 injections of novarsenobenzol in doses of from .6 to .75 gram, followed by the mercurial pill treatment.

Mercurial treatment should be given 20 days per month, during 3 months, after the first salvarsan course; 12 to 15 days per month for the next 9 months; and during the following year, 12 to 15 days every second month; 40 to 50 days twice during the third year; 40 to 50 days twice in the fourth year; and 40 to 50 days twice in the fifth year; thereafter, 40 to 50 days once yearly.

This treatment should be continued practically throughout life, to assure the patient against possible relapse. It will do the patient no harm and if he has small foci of *Treponemata pallida* in his bones, in his liver, or in his heart muscle, this treatment will neutralize their effects and keep them clinically latent.

If the patient can see his physician frequently, he should have either **intramuscular injections of gray oil or salicylate** once weekly, **or intravenous injections** every other day, in courses as outlined above.

D. Treatment of Syphilis during Pregnancy.—The treatment of syphilis during pregnancy does not materially differ from the general treatment of syphilis. There are, however, several factors which deserve special attention: *First,* the protection of the mother from the grave symptoms which are so common during pregnancy. It is well known that syphilis is more grave, as a rule, during pregnancy than at any other time. No doubt, the physiology of pregnancy, which, after all, must be considered somewhat of a pathology, has much to do with this, because of the gross changes which occur in all the tissues of the body during this time. *Second,* and of great importance, is the effect which syphilis of the mother has upon the unborn child. The medical profession is well aware of the high mortality in infants born of syphilitic mothers;

only benefits the mother herself, but is also a true life-saver for the unborn child.

PROGNOSIS

The prognosis of syphilis is variable. With modern treatment, grave symptoms are not so frequent. Osler makes the statement that, in general, the prognosis of the average case is good with careful treatment and bad without it.

There are several factors which influence the prognosis. The *patient's general condition* is one of the important factors. A patient who is strong and robust and has always enjoyed good health is in a much better position to combat the syphilitic infection than a person whose health is generally poor and whose physical condition is not at par. An individual in otherwise perfect health is better able to tolerate the intensive treatment necessary to kill the *Treponemata pallida.*

The *presence of any intercurrent disease* is a serious complication and renders the prognosis much more grave, as now the patient has two or more forces tending to break him down, either one of which is about all that can usually be combated successfully.

Age is an important element in the prognosis. The mortality and morbidity among children is very high; it is also quite high in the aged. Old age predisposes to severe skin eruptions and also major nerve involvement. The excretory organs of old persons function poorly, and consequently it is sometimes difficult to administer sufficient treatment; hence the prognosis is less favorable.

Intoxication, such as alcoholism, plumbism and excesses of all kinds render the prognosis less favorable. These intoxications lead to a marked reduction in the patient's vitality and consequently enable his syphilitic disease to progress and spread.

The use of *tobacco* may be responsible for mouth lesions and should be stopped, at least during the first few months of the disease.

There are certain *hereditary predispositions,* especially those concerned with the nervous system, which are a grave factor, since they favor the production of tabes, general paresis and other complications.

A *neurasthenic or hysterical person* may become so troubled over his condition as to become much depressed mentally and be quite indifferent to his mode of living, treatment and exercise—which factors are very essential to good recovery. The patient must have the *will to get well* and undergo treatment. The facts must be presented in such a way that he will understand the seriousness of his disease and at the same time understand that the prognosis depends absolutely upon himself. If he accepts the advice of his physician and follows his instructions, the prognosis is excellent; if he does not, the prognosis is very poor.

The *amount of treatment* which the patient receives and the *time when treatment is begun,* are of great importance. The prognosis is decidedly better—both as to recovery and guarantee against recurrence —in a case which is *diagnosed in the early days of the disease,* when the Wassermann reaction is yet negative, than it is in a case with cutaneous eruptions and a positive Wassermann. The treatment must be thorough and regular; the patient not dismissed as cured until blood-tests, repeated at various intervals, are negative and he has been free from symptoms for some time. The insufficiently treated cases are very frequently followed by grave recurrences; and the prognosis in a case which is not at all treated is very bad.

The *lapse of time during which the patient is free from symptoms* is a factor in the prognosis. If he has been free from symptoms for a period of 1½ to 2 years following treatment, we can be relatively sure of his cure.

The length of life, according to statistics, based upon life insurance, would indicate that life is shortened about 5 years through the invasion of syphilis, and that about 1/7 of the syphilitics die as a result of their infection, from 20 to 30 years following the infection.

PATHOLOGY

The *Treponema pallidum* enters the body through a break in the epidermis. This break may be microscopic in size, but once the organism enters, it soon proceeds to invade all body tissues by way of the lymph and blood-streams. The body tissues immediately undergo a change and attempt to combat the invasion, by making the conditions less favorable for the *Treponemata pallida* to multiply. However, the spread of the organism is very rapid and the infection soon becomes generalized. It has become generalized long before the appearance of secondary lesions.

The organism appears to have a predilection for certain tissues, such as the blood-vessels, bone and nervous system, kidneys and other viscera. It is not infrequent that the bone marrow is invaded very early. Whether the *invasion of a special tissue* is purely accidental or whether there are various strains of the organism which select this particular tissue is as yet not definitely settled, but work done by recent investigators seems to indicate the existence of strains of *Treponemata pallida* that attack different tissues. However, the *resistance* which the patient offers to the invasion must also be considered as a possible factor in determining the type of the tissue invaded. The clinical observation —that patients suffering with syphilis of the nervous system usually give no history of a secondary rash and that patients having syphilitic ostitis and periostitis are not frequently affected with skin lesions— rather supports such a belief.

During the early period of infection, the organisms are practically free in the tissues. Soon, however, the invading organism produces gross changes—principally of a fibrous nature—in the invaded tissues. The structure and function of the invaded tissue are impaired in direct proportion to the amount and location of the tissue change.

Recent investigations done by Wile have shown that the invasion of the central nervous system is relatively early in the secondary stage. Invasion of the central nervous system may manifest itself early in the disease or remain latent for a considerable period. Wile determined that there was an early involvement of the central nervous system in 30 per cent. of cases, while Fordyce states that no more than 20 per cent. of his cases of early syphilis show invasion of the central nervous system. Wile also detected early invasion of the bone.

The *Treponema pallidum* does not multiply readily in the blood, but adapts itself much better to the lymph. The organisms become localized in the lymphatic spaces, especially in the lymphatics draining the infected area. The body tissues may offer considerable resistance to the growth of the *Treponema pallidum*, resulting in an infiltration of round cells and proliferation of connective-tissue cells around the invading organisms, thus giving rise to the chancre.

Primary Stage.—The chancre is distinctly neoplastic in type. It sometimes begins as a small vesicle, but usually as a light thickening or induration of the surface tissue. The epithelium usually becomes necrotic, falls off and reveals a shallow ulcer. Quite early in the development of the chancre, numerous capillaries are formed. A cellular infiltration occurs, especially in the region about the blood-vessels. These cells are chiefly mononuclear cells, of the type of lymphocytes. Plasma cells and large mononuclear and polymorphonuclear leukocytes are also present. The intima of the blood-vessels becomes decidedly thickened. The ulcer may become deep and extensively involve a considerable area of skin. However, it heals ultimately. The induration disappears and only the scar remains.

Secondary Stage.—The *rash,* which is a characteristic lesion in the secondary stage, appears as a macular, papular, vesicular or pustular eruption. When these heal they leave little trace of their presence, rarely producing a scar, but occasionally leaving an increase in pigmentation.

The *macular syphilid* is the first one to appear subsequent to the chancre. It appears first on the trunk and rapidly appears over the entire body. There is a slight dilatation of the blood-vessels of the skin and a very slight cellular infiltration occurs.

The *papular syphilid* shows distinct and more advanced changes. The lesions are somewhat elevated, due to a marked local cellular infiltration; namely, dense, vascular infiltration of mononuclear leukocytes, together with a thickening of the vessel walls themselves. When the papule disappears, a slight discoloration frequently remains for some time. Scales may cap the papules or pustulation, and crusting may occur.

The appearance of *mucous patches* in the mouth is very characteristic of syphilitic lesions of the secondary stage. These occur as white areas located in the mucosa. At first, they are raised; later on, they become oval, circumscribed ulcers. The white color is due to a thickening of the epithelium; the ulcer appears when this thickened epithelium sloughs off. Mucous patches may occur on any mucous surface.

Flat *condylomata* frequently occur in the region of the genitals, about the anus and inner aspect of the thigh or any moist surfaces which are opposed to each other. Condylomata consist of round, broad, lobulated elevations. The epithelium is thickened and there is cellular infiltration, chiefly of the lymphocyte type of cells.

Tertiary Stage.—The *gumma* is the characteristic lesion of the tertiary stage. It varies in size from microscopic to the size of a hen's egg. It consists of a mass of small spheroidal and epithelioid cells. As the gumma increases in size it is likely to become necrotic and caseous at the center. Grossly, it appears as a grayish-white or yellowish mass which is firm, elastic and transparent. The periphery is definitely circumscribed and radiating connective tissue fibers are seen surrounding it. Characteristic changes are produced in the blood-vessels, such as endarteritis and panarteritis.

Following the inoculation and the generalization of the infection, the patient develops a sort of *immunity.* This immunity, however, is only relative since, if sufficient virus is used in making an inoculation, a lesion develops which is atypical and insignificant. Such a lesion will result even during the secondary stage of the disease. If inoculation is made in the tertiary stage, a tertiary lesion will result.

Circulatory System.—HEART.—In cardiac syphilis, the pericardium, myocardium or endocardium may be affected. The affection may manifest itself as a hyperplastic infiltration or as a gummatous involvement. Syphilitic pericarditis usually manifests itself as a fibrous pericarditis, affecting only a small portion or the greater part of the pericardial sac. Gummata of the pericardium are occasionally found and occur as miliary lesions, scattered over the pericardial surface. Myocarditis may occur as a fibrous or gummatous process and leads to weakening, dilatation and hyperplasia of the heart wall. Syphilitic endocarditis only rarely affects the valves. When there is vascular involvement, only one valve is attacked, and usually only one of the cusps. The left ventricle and septum are most commonly affected. Fordyce states that 75 per cent. of aortic insufficiencies are syphilitic in origin.

ARTERIES.—The syphilitic infection begins in and about the arteries; consequently, they are extensively involved during the course of the disease. Syphilitic aortitis is responsible for the great majority of cases of aortic insufficiency, aortic dilatation and aneurysms of the aorta. Syphilitic aortitis affects chiefly the ascending portion of the aorta in the region of the valves. The process spreads from this region and later involves the valves. Aortitis may affect the descending aorta, and if the sclerosis is extensive, the abdominal aorta may also be involved. Macroscopic examination of the aorta reveals very characteristic pictures; the internal surface appears wrinkled and puckered. Radiating elevations are present and there is a tendency to sclerosis. Uniform or fusiform dilatation of the aorta may occur. Aneurysmal pouchings may occur or true aneurysm may exist. The various layers of the vessel walls may vary considerably in consistency and thickness. Some areas may be thin and translucent and others may be thick and cartilaginous. The intima maintains its characteristic glistening appearance.

Microscopic examination shows the infection to involve the blood-vessels themselves. The walls of the vessels become thickened and there is a surrounding infiltration of lymphocytes and plasma cells. The media of the vessel is affected by a miliary gummatous process. Fragmentation occurs and is followed by destruction and disappearance of the elastic tissue fibers.

The cerebral arteries are frequently involved. The process consists in the development of a nodular tumor, associated with a gummatous meningitis or with the presence of many large gummata. The artery may be extensively involved by the gummatous process and proliferation result. Thickening of the layers of the arterial wall in the smaller vessels may produce obliteration with or without thrombosis. Obliteration of the vessel lumen produces various pathological conditions, depending upon the artery involved. In case one of the cerebral arteries is affected, a paralysis, hemiplegia or monoplegia will result; whereas if one of the arteries of the extremities is involved it may produce a gangrenous area.

CAPILLARIES.—Syphilitic disease of the capillaries consists of a swelling of the endothelium, with an infiltration of lymphocytes and plasma cells. The process is so closely related to the changes in the various organs that it is better described with them.

Lymphatic System.—Enlargement of the lymph nodes occurs early in the course of syphilis. Taken in connection with the presence of a chancre, lymphatic enlargement constitutes one of the earliest diagnostic signs of a syphilitic infection. The nodes are hard; the lymphatic ducts, when palpable, feel hard and cord-like. Invasion of the lymphatic system may be very extensive during the secondary stage, or almost entirely absent. The degree of involvement is no indication as to the severity of the disease. The regional glands are the ones first and most extensively affected. The epitrochlear glands are two deep lymphatic glands of considerable importance, as they are deep, from the lymph circulation standpoint, but superficial and easily palpable from an anatomical standpoint. Consequently, they only enlarge from some constitutional disease and not from superficial infections.

Respiratory System.—NOSE.—Primary syphilis of the nose is rare. Occasionally mucous patches are found on the inferior turbinate at its anterior extremity or on the inner aspect of the alæ. The posterior nasal space is most frequently attacked by secondary lesions. The membranes of the nose appear congested.

In the tertiary stage, the nose may be involved very early, principally by ulcerative lesions. The ulcerations spread slowly and leave large suppurative areas. The degree of involvement may be deep enough to cause the septum to be perforated, and if the perforation is large enough the support of the nasal bridge is weakened and the nose caves in.

LARYNX.—Syphilitic involvement of the larynx is rather rare. In a series of 341 cases of late syphilis, Symmers found it in about 4.5 per cent. of the cases. The disease manifests itself in the secondary stage as mucous patches, which may or may not be ulcerated, or as condylomata. In the tertiary stage, laryngeal syphilis manifests itself as a diffuse infiltration of small round cells which may ulcerate or may become organized and produce a swelling which usually affects the vocal chords, the perichondrium or the arytenoid folds. Laryngeal gummata are observed invading the epiglottis and the posterior portion of the larynx. The perichondrium may be affected and result in necrosis or exfoliation of the affected cartilage.

BRONCHI AND TRACHEA.—During the primary and secondary stage of syphilis involvement of the trachea and bronchi is catarrhal in nature, and no definite pathological changes are observed. In the later stages, gummatous involvement may be quite extensive and lead to a series of changes, from thickening of the mucosa up to and including ulceration, cicatrization and resultant stenosis.

LUNGS.—Syphilis of the lungs is very rare and is seldom diagnosed clinically. It occurs as the congenital form—so-called white pneumonia —which is a diffuse pulmonary change of an interstitial type. It is seen in stillborn babies or babies who live but a short time. Or it may occur as the acquired form, rather sharply circumscribed. The latter is usually gummatous in nature, or it may be a chronic interstitial pneumonia or syphilitic phthisis.

One lobe of the lung is usually affected in part or whole. The lung appears white or grayish-white in color. It is heavy and dry and may be free from air if the child is stillborn. Thickening of the alveoli is present. In interstitial pneumonia there is an extensive infiltration of the interalveolar connective tissues. Connective tissue of the interalveolar areas becomes markedly increased. The characteristic syphilitic arterial changes are observed.

In the acquired type of lung syphilis, the gummata resemble in every way the gummata found in other organisms, but generally white-scar tissue develops and leads to a contraction of the lung tissue. Interstitial pneumonia is manifested by long strands of connective tissue which radiate from the hilus of the lungs and may surround the bronchi and blood-vessels. The lobe of the lung may be extensively involved or only areas of sclerosis may occur. Syphilitic phthisis is very rare. The process usually develops about the root of the central portion of the lung and progresses in any direction. The gummata rarely break down and there is very little tendency toward cavity formation. When cavities are present they are usually bronchiectatic in type.

PLEURA.—The pleura may be secondarily involved in syphilis of the lung and become thickened. Gummatous infiltration of the pleura has been described. It is exceedingly rare.

Digestive System.—SALIVARY GLANDS.—Tumefaction of the salivary glands occasionally occurs during the secondary stage of syphilis. The parotid gland is most frequently involved and the condition simulates mumps very closely. Fordyce relates the case of a patient in the tertiary stage of syphilis who consulted him for a diffuse hyperplasia of the parotid glands. His infection dated back eight years. He had a marked interstitial glossitis that manifested itself by great enlargement of the tongue with deep fissures and patches of superficial leukoplasia. Swelling was perceptible in both glands. The consistency was increased and there was no tenderness. The glandular enlargement subsided gradually under antisyphilitic treatment.

ESOPHAGUS.—Gummata of the esophagus most frequently involve the lower portion of the passage. Diffuse infiltrations are more marked in the central region. These processes are followed by inflammation and cicatrized tissue, and ultimately result in a stenosis of the esophagus.

STOMACH AND INTESTINES.—Acute syphilitic enteritis has been reported from time to time, but little is known of the condition. Chronic enteritis, however, occurs during any of the stages. It consists of an infiltration of small round cells in the stomach walls and an increase in connective tissue. Gummata of the stomach and intestines occasionally occur and may be very circumscribed or diffuse in type. Occurrence of syphilitic ulcerations is rare; Symmers reports 1 case of undoubted syphilitic ulcer in 314 necropsies in syphilitic cases. This case showed characteristic histological features of syphilis, such as chronic proliferation, inflammatory changes, miliary gummata, endarteritis obliterans and cellular infiltration. The organism most frequently attacks the large intestine. Chancres may occur in the rectum or diffuse gummata may be observed, which ulcerate and lead to a stenosis or perforation.

LIVER.—Acute hepatitis may be caused by syphilitic infection during the secondary stage of the disease, but since few of these patients die during this stage, the specimens of such conditions are relatively rare. Jaundice occasionally occurs at the time of the skin eruption, and acute yellow atrophy sometimes occurs, which consists in a rapid degeneration of the parenchyma. Various theories have been formulated to explain the occurrence of jaundice, such as pressure on the bile duct by the enlarged lymphocytes, and inflammation of the duct, acute hepatitis with hyperemia and stopping-up of the bile duct by syphilotoxin.

Syphilitic hepatitis in infants who have had congenital syphilis has been carefully studied. It is quite likely that the acquired and congenital types are more or less similar. In case of congenital hepatitis, there is a diffuse cellular infiltration of the parenchyma, chiefly with mononuclear cells. The infiltrations may be perilobular, lobular and interstitial in type. The liver is increased in size and cholangitis and cirrhosis of the liver may be noted.

The changes in the liver which occur later in the course of syphilis are better known and the pathological lesions resemble more closely those produced in other parts of the body. Gummata and fibrosis are characteristic manifestations. The syphilitic liver may be grossly divided into three types; all three types may be present in the same liver.

(*a*) *Lobulated Type of Syphilitic Cirrhosis.*—The lobulated type of syphilitic cirrhosis is frequently characterized by gummata. Lobulation is produced by the absorption of the gummata and their subsequent replacement by fibrous tissue. These lobulations may be few or numerous. The left lobe is usually more extensively involved than the right lobe.

(*b*) *Diffuse Type of Syphilitic Cirrhosis.*—This type presents characteristic lesions of syphilitic perihepatitis on the surface of the liver. The lesions consist of grayish or whitish scars which are more or less stellate in shape. These scars are usually deep, and thus interrupt the otherwise smooth surface of the liver. The fibrous changes produced extend into the parenchyma or may be attached to the hepatic capsule. A diffuse fibrosis is observed scattered throughout the organ.

(*c*) *Perihepatitis.*—This type of syphilitic liver involvement is characterized by stellular or lobular fibrosis on the surface of the liver. They may be grayish or whitish in color and vary greatly in size from a few microns to several centimeters. There is no parenchymatous involvement, except in the region immediately beneath the capsule. Symmers reports that in 4,880 necropsies—of which 314 were cases of fatal syphilis—syphilis of the liver, manifested as lobulated cirrhosis, was present in 16 per cent. Syphilitic scars were found on the liver in 6.8 per cent. and amyloid disease was present five times.

PANCREAS.—The pancreas is only rarely involved by syphilis. Pancreatitis is more common in adults than gummata. It occurs as an induration which simulates syphilitic cirrhosis of the liver and is usually associated with the latter condition. A palpable tumor may be present which leads to obstruction of the pancreatic ducts and occasionally the common duct. Warthin, however, states that in all the old cases of syphilis which he examined at autopsy the pancreas showed greater or lesser degree of atrophy and interstitial fibrosis. In the majority of cases, the changes occur through the organ; but it undoubtedly shows special tendency to involvement. Some of the lobules showing marked changes were surrounded by lobules showing no changes, while in other cases the entire pancreas showed a diffuse fibrosis.

The increase in connective tissue was intralobular and interlobular. Careful examination in each case revealed the presence of active areas of plasma-cell infiltration, and in a few cases, the presence of *Treponemata pallida.* The syphilitic nature of the lesions was known from the syphilitic lesions in other tissues. Of 12 cases of diabetes which were autopsied by Warthin, the pancreas showed characteristic plasma-cell infiltration and fibrosis in 11 of them. In all but 2 cases, island fibrosis was very marked; however, in several non-diabetic cases, chronic pancreatitis and fibrosis of the islands were equally or more marked. Warthen considers these changes as characteristic of syphilis involving the pancreas.

PERITONEUM.—The peritoneum when involved is always secondary to syphilitic disease in some of the abdominal viscera.

Urinary System.—KIDNEY.—The kidneys are affected both during the early and late stages of syphilis and also in the congenital and acquired form. Albuminuria is frequently observed during the early or secondary stage. It is usually persistent and may be very severe. The urine may contain albumin for a considerable period. The nephritis may be of an acute or subacute type, which usually ends in recovery; or a chronic characteristic tubular type may result and lead to the production of a large white kidney, and seriously involve the excretory tubules.

In the tertiary and latent stages, syphilitic nephritis is more common. Acute and chronic parenchymatous or interstitial nephritis may occur, as well as amyloid degeneration. Interstitial nephritis is more common than the parenchymatous type. It consists in a marked increase in connective tissue of the kidney and capsule, with an obliteration of the tubules by compression. The walls of the blood-vessels are very much thickened and induration is very marked. Gummata rarely occur; they are usually multiple and located in the cortex or pyramids. A large solitary gumma may occur and closely simulate tumor. Amyloid disease is frequent in the older patients.

URETERS.—Syphilitic infection of the ureters is very rare.

URETHRA.—The urethra may be the seat of syphilitic infection during any stage of the disease. It is most frequently involved during the primary stage, when inoculation may occur at the meatus or fossa novicularis. Mucous patches sometimes develop in the urethra during the secondary stage. During the tertiary stage, the urethra may be invaded by a diffuse gummatous inflammation, with ulceration; or by a solitary gumma, which is less common.

BLADDER.—The bladder is affected both during the secondary and tertiary stages of syphilis. During the secondary stage, the mucosa appears congested and lesions similar to mucous patches may be observed cystoscopically; while in the tertiary stage gummata and ulcerations are observed. They project into the cavity. Their edges are infiltrated, and they are usually covered by incrustations.

Reproductive System.—UTERUS.—Syphilis of the uterus is rare. Primary and secondary lesions of the body of the uterus, as yet, have never been observed, but several cases of tertiary lesions are recorded. The changes produced are gummatous in type. Chancre on the cervix is a relatively common lesion. Schwarz reports a case of late syphilis of the cervix uteri in a patient who was operated upon. At operation, the uterus was found to be at least twice the normal size. It was indurated and oozed freely. There was no apparent ulceration present. Examination of the tissues obtained by curettage showed nothing more than a chronic endocervicitis. However, the cervical tissue showed an inflammatory condition. There was evidence of round-cell infiltration. Diffusely scattered through the tissue were cells which stained slightly and whose outline was distinct. Four or five giant cells were observed in a field. The infiltration was especially marked around the blood-vessels, and in some places induration of the muscle tissue was observed. The patient gave a positive Wassermann reaction.

MAMMARY GLAND.—The mammary gland may be affected during any stage of acquired syphilis. It is also affected in congenital syphilis.

Chancres or mucous patches may occur on the nipple. In the tertiary stage and in congenital syphilis, the gumma is the characteristic lesion.

PROSTATE.—The prostate is seldom affected in syphilis. When infection does occur in this gland, the lesions are analogous to the syphiloma in other locations. The lesions are of the tertiary type only and are destructive in nature.

OVARIES.—Gellhorn and Ehrenfest, after collecting records on a considerable number of cases, report a supposed syphilis of the ovary and conclude that in only one case was there positive proof of the existence of a syphilitic process. This was a case reported by Hoffman in which the Wassermann was positive. At autopsy, the right tube and ovary were transformed into a gummatous mass, and a thick layer of gummatous tissue was found which involved the entire endometrium and penetrated deeply into the myometrium. Gummata were also found in the liver and lungs.

TESTES.—Syphilis frequently attacks the testes. There may be an involvement in both the acquired and congenital types of the disease. Involvement of the epididymis and the membranes is usually secondary and manifests itself as a diffuse induration of the testes, with or without hydrocele. It also manifests itself as circumscribed gummata. The testicular tubules are compressed, degenerated and atrophied, and may present a cheese-like appearance. When the membranes of the testicles are involved a diffuse thickening occurs. The vas may be greatly thickened, and hydrocele occurs in the secondary period at the time of the appearance of the skin rashes. Later on, in the tertiary period, hydrocele occurs as a complication of testicular gummata.

Nervous System.—BRAIN.—Meningitis occurs both as a hyperplastic and as a gummatous process, involving all of the membranes of the brain. The process may be the extension of the disease from other tissues, such as an ostitis or periostitis, which later involves the dura. A diffuse gummatous infiltration, usually associated with a fibrosis hyperplastic meningitis, is usually found where the meninges are primarily involved. The process usually remains as a leptomeningitis, even when the three membranes are involved. Syphilitic meningitis is uniformly distributed over the base and the convexity of the brain but it may be localized. In a syphilitic leptomeningitis, or pachymeningitis, the base of the brain seldom escapes. The region about the chiasm and the interpeduncular area are the sites most frequently affected. This leads especially to the involvement of the optic nerve and the muscles of the eye. Small or large gummata may be present; they may be single or multiple or occur as a diffuse infiltration. The base and the convexity of the brain are usually the sites of their occurrence, and they usually appear on the dura. When they are present in the brain substance, they are usually located in the cortex and generally in the region of the central convolution; but they are not limited to this area.

The blood-vessels may be invaded by the syphilitic process, to the extent of narrowing or even complete obliteration. Interference with the blood supply may lead to softening and necrosis of the arterial areas supplied by the blood-vessels. The internal capsule, pons, medulla and large ganglia, because of their terminal blood supply, are especially liable to softening. Cerebral hemorrhage may also occur as a result of rupture, due to degenerative changes in the blood-vessel walls.

CORD.—Spinal syphilis may be a disease of the meninges, nerve roots or blood-vessels. The changes produced in the cord itself are secondary to and dependent upon the pressure from the thickened meninges or the anemia produced by the blood-vessel changes. The meninges may be invaded and gummatous thickening or tumor formation occur. The process may extend to the periphery of the cord and involve the nerve roots, producing severe pain. Endarteritis, endophlebitis and thrombosis may cause disturbances in a part of the cord, with the production of local softening and necrosis.

NERVES.—Because of the position of the cranial nerves at the base of the brain, they are frequently compressed in the foramina as they leave the skull, by a thickening of the meninges. The oculomotor nerve is involved in nearly one-half of the cases, and the branch supplying the levator muscles of the upper eyelid is especially involved, producing ptosis. Optic neuritis is frequently present and leads to atrophy and blindness. The trigeminal may be involved in any one or all of its branches and may produce disturbed sensations. Facial palsy may occur alone or associated with deafness on the same side. The peripheral nerves may be affected during syphilitic infection and the lesion produced varies with the nerve involved, the location of the lesion in the nerve, the nature thereof, and its extent. There may be actual destruction of the nerve tissue, leading to muscular paralysis, in case of involvement of the motor nerve, and sensory loss in case a sensory nerve is involved.

Muscular System.—Syphilis of the muscles occurs as a diffuse syphilitic myositis or as a gummatous process. Diffuse syphilitic myositis, early, consists of a swelling of the muscle with a deposit of plastic material between the muscular fibers. Later, fibrosis occurs and atrophy of the muscle fibers results. There is an increase in the interstitial connective tissues, with separation of the muscle fibers from each other. The muscle fibers may later become opaque, granular and the striation disappear, or, if simple atrophy results, the striation will remain well marked.

Gummata, when recent, are not sharply defined from the surrounding muscular tissue, but in the later types a cellular infiltration separates the gumma from the muscular tissue. The muscle fibers are somewhat separated from each other and are partially atrophied. In most cases, the fibers retain their striations and nuclei, but in older cases dense fibrosis may be present. Atrophy of the muscle tissues in either case leads to contraction.

Bones and Joints.—OSSEOUS SYSTEM.—Periosteal inflammation may occur during the secondary stage of syphilis; but the tertiary lesions of the bones are far more common. The skull, tibia, fingers and such bones as are rather superficially located are most commonly affected.

The lesion produced may be distinctly gummatous or it may closely simulate chronic inflammation of the bone, such as is observed in other diseases. The periosteum is first involved; it becomes more or less separated from the bone by an inflammatory infiltration, which is composed, for the most part, of small, round cells. Occasionally, the periosteum ruptures and produces a break in the skin. Ulceration may become quite extensive and may lead to necrosis of the bone and the formation of a sequestrum which may be discharged. Instead of ending with ulceration, however, the syphilitic inflammation may lead to the production of new growth of spongy bone on the old cortex. The bone may, on the other hand, become very hard and solid. The production of new bone tissue on the outside of the shaft causes a thickening of the bone and produces a rough and irregular surface. When the production of new bone is very extensive and, besides invading the periosteum, invades also the haversian system and the cancellous portion of the bone in the interior, the bone may become very dense and ivory-like. Such bone is much heavier than normal.

Gummatous lesions may affect the periosteum or the interior of the bone. When the periosteum is affected, the process extends along the blood-vessels, enlarges their canals and, by the process of erosion, gives them a peculiar worm-eaten appearance. If such process is very extensive, complete destruction of the bone may result. In case the skull is involved, a gummatous mass may penetrate it sufficiently to lead to involvement of the dura mater or it may even extend deeper. Osteophytes from the periosteum surround the process and make it appear still deeper. The shin bone may be the seat of gummatous nodes which extend into the cortex and marrow cavity and may lead to necrosis of the bone fragments.

The skull may be extensively involved. Both rarefaction, with destruction and sclerosis of the bone, may result simultaneously in such a process. Involvement of the bone marrow by gummata is not infrequent; it consists of gelatinous patches which, because of their fat content, often appear bright yellow in color. These patches may occur singly or they may be sufficiently numerous to fill the whole marrow cavity. Usually they do not give rise to any outward evidence of their existence, but the cortex may be eroded and a corresponding new layer of bone may be produced by the periosteum. Fistulæ or canals are formed which resemble very closely the lesions produced in an ordinary osteomyelitis, except that no sequestra are present. Gummatous osteoperiostitis with enlargement, rarefaction and internal destruction of the phalanges is observed in syphilitic dactylitis.

JOINTS.—The joints may be attacked in the course of a syphilitic infection. Involvement may manifest itself simply as an accumulation of water exudate or by the formation of granular tissue in the synovial membrane which may later become ulcerated. This involvement may be secondary to the epiphyseal involvement. The cartilage becomes raised and the cavity may become obliterated by the fibrosed tissue.

BONES IN HEREDITARY SYPHILIS.—The lesions found in acquired syphilis are also found in hereditary syphilis, but many of these processes in children have more special features. Bone forms under the periosteum, which is very characteristic and gives rise to nodes. The nodes are at first soft, but later become sclerosed, and unless antisyphilitic treatment is begun early they are quite likely to persist indefinitely.

Syphilitic osteochondritis is characterized by the ends of the bone becoming enlarged. This enlargement usually occurs within the first year of life and affects, chiefly, the epiphysis. *Separation of the epiphysis* may occur as a result of the transformation of the cartilage into connective tissue. The affection is usually symmetrical; it may be multiple. The knees, elbows and wrists are most frequently attacked.

The *epiphyseal line on the femur* presents a very definite picture in hereditary syphilis. In the hereditary syphilitic bones, the line between the epiphysis and diaphysis is broad and uneven, instead of narrow, sharply defined and regular, as in normal bone. Various grades of the lesion may be observed. If the involvement is only slight, a white or reddish-white zone which is very irregular, broad, and consisting of calcified cartilage with an abundance of cartilage cells, may exist between the cartilage and the newly formed bone. If the lesion is more severe, the zone is still broader, more irregular and less sharply defined from the zone of ossification. The surrounding cartilage is rather soft; many blood-vessels, areas of connective tissue, calcification, or irregular ossification, may be observed.

Craniotabes is very characteristic of hereditary syphilis and consists of an absorption of the osseous tissue of the cranium, forming here or there a thin bone; or the bone may be entirely absorbed in places. The parietal bones are most frequently affected.

Endocrine System.—SUPRARENALS.—Amyloid degeneration of the suprarenal glands is not uncommon. Interstitial changes take place and localized or diffuse gummatous inflammations are observed. The cellular infiltration, so characteristic of syphilitic processes, is slight, in the majority of cases. The medulla on the inner portion of the reticular zone of the cortex is generally affected. The capsule is usually thickened, and infiltration and fibrosis may be so extensive as to cause marked atrophy of the gland, simulating Addison's disease. Gummata are frequently present and are usually miliary in type. *Treponemata pallida* are abundantly present in congenital syphilis, involving the parenchyma.

THYMUS.—Up to the present time, but little is known about syphilitic infection of the thymus. Various cases of such infection have been reported from time to time, but the subject is still open to investigation.

THYROID.—The thyroid gland is very frequently enlarged in early secondary syphilis. Gummata rarely occur, either in adults or in the newborn.

PITUITARY.—Little is known about the syphilitic involvement of the pituitary gland during the early stages of syphilis. In the tertiary stage, the gland may be invaded by a gumma and produce glycosuria or other pituitary symptoms.

Blood.—Oligocythemia and oligochromemia occur when there is extensive glandular involvement. Anemia of the chlorotic type and marked hemoglobin reduction are common at the outset of the secondary symptoms and are also present late in the disease when numerous ulcerations are present. There is a slight increase of white cells, especially the lymphocytes. A slight eosinophilia may be observed. *Treponemata pallida* may be found in the blood rarely.

Skin.—The lesions which characterize a syphilitic infection are the *chancre* in the primary stage, the *rash* in the secondary stage and *gumma* in the tertiary stage.

Organs of Special Sense.—EYE.—The *conjunctivæ* may be involved during any stage of the disease, but such involvement is extremely rare.

The *cornea* is frequently affected and the infection manifests itself as a keratitis. It may be produced either in the acquired or hereditary syphilis, but it is more common in the latter type of the disease. The cornea becomes more or less opaque, due to a thickening of the epithelium and to infiltration of leukocytes.

Syphilitic iritis develops frequently early in the secondary stage, but may appear late and be due to minute gummata. The *choroid*, when invaded, manifests itself as a serofibrinous process, or a diffuse or disseminated choroiditis. Involvement of the retina is usually associated with this condition. The vitreous appears cloudy; connective tissue formation leads to atrophy.

EAR.—Syphilis may affect any part of the ear. The *drum* is occasionally the seat of a primary infection. The *labyrinth* is sometimes affected during the secondary stage, probably as the result of vascular changes or of a periostitis, and is usually unilateral in type, and acute or chronic otitis may be observed. The *internal ear* may be secondarily involved and may be the seat of secondary or tertiary lesions.

HEREDITARY SYPHILIS

Hereditary syphilis differs from the acquired type of the disease chiefly in the *absence of definite periods in the course of development.* Chancre never occurs, and the disease, to begin with, is a constitutional one. Hereditary syphilis may be early or late, depending upon the time which elapses before syphilis manifests itself. In early hereditary syphilis, the symptoms may be present at birth or they may appear within a few days or weeks. As a rule, the child appears normal at birth and continues so for a variable time before the syphilitic infection manifests itself. Where the infection is severe, the symptoms are present at birth or soon develop. In late hereditary syphilis, the child may appear healthy for several years, even up to the fifteenth or twentieth year, before any symptoms appear.

Transmission.—It is now very generally believed that the transmission of syphilis is from the mother to the child through the placenta, the fetus thus becoming infected in the uterus. Infection may occur at the time of birth, but such infection is really acquired syphilis and the symptoms do not especially differ from those of acquired syphilis in the adult.

Factors Which Determine the Development of Hereditary Syphilis.—The development of syphilis is determined by several factors, such as the time of pregnancy during which infection occurs, the stage of maternal syphilis during which infection occurs, and whether treatment has been administered to the mother before or during the pregnancy. If the mother becomes infected during the early months of pregnancy, abortion is most likely to follow, whereas if infection occurs in the later months of pregnancy, the chance for abortion is less, or the child may even escape infection completely. If conception occurs a short time following the infection, abortion is likely to occur, while if the mother's syphilis is fairly late, the child may be born at term as a macerated fetus or as a stillbirth, or it may even be borne apparently healthy.

Characteristic Symptoms of Hereditary Syphilis.—The syphilitic child presents a very characteristic appearance at birth. It appears weak, feeble, and the skin presents a dirty appearance and eruption may be present on the palms and soles. The face presents the appearance of a little old man. Coryza is present and the cry is weak and hoarse. The physical features are poorly developed or may even be abnormal. The majority of syphilitic children, however, produce no such characteristic appearance at the time of birth and the symptoms do not present themselves until about two or three weeks after birth, the child appearing well nourished and well developed until that time.

CORYZA.—Nasal catarrh is a very characteristic symptom in the majority of congenitally syphilitic infants. It is usually early, preceding the skin eruption, and lasts for some time after the other symptoms of syphilis have disappeared. Breathing becomes difficult and the child snuffles. This difficulty in breathing is the result of congestion and swelling in the nasal mucous membrane, which may be extensive enough to almost completely close the nasal passages. The real obstruction, however, is due to the presence of a nasal discharge, which consists of mucus and serum and which later becomes blood stained. Persistent discharge causes irritation of the lips, which become red and excoriated. As time goes on, the discharge becomes more profuse, crusts, and forces the child to breathe through its mouth because of complete nasal obstruction. If treatment is not administered early, the submucosa may be involved and ulceration results. Still later in the disease, the nasal cartilages and bones may become infected.

SKIN ERUPTIONS.—Skin eruptions of hereditary syphilis in general simulate fairly closely the lesions observed in acquired syphilis. Nevertheless, there are certain differences in the course and the symptoms produced which serve to differentiate them. The initial lesions are never observed, and the appearance of the eruption is not characterized by definite periods. However, the nature of the syphilid depends upon whether the infection of the fetus occurred before or after conception, or whether it occurred at the time conception took place. The nature of the skin also serves to determine the type of eruption. Infiltration is less marked than in acquired syphilis, but hyperemia is more intense. When the eruption occurs late in the disease, the lesions more nearly resemble those observed in adult infection.

Erythematous or Macular Syphilid.—The erythematous or macular syphilid is the lesion most commonly observed. It may appear within one week after birth, or as late as two months or more, but on the average it appears within the first month. The macular eruption manifests itself as red patches, which later become brownish-red in color. They appear on the body in the form of small, oval, rounded or irregular spots, which do not entirely disappear on pressure. The eruption may be somewhat confluent and cover considerable areas, forming a more or less unbroken sheet which is dull red in color. The genitals and face are not infrequently involved and in this way they differ from the macular syphilid observed in acquired syphilis.

Papular Syphilid.—The papular syphilid, which occurs in hereditary syphilis, is less infiltrated than that observed in acquired syphilis. The tendency toward scale formation is also less marked. When the papules are situated on the surfaces which are constantly moist and irritated, they give rise to mucous patches, or condylomata lata. These lesions are especially found in the region of the mouth and anus, on the thighs or scrotum. Ulceration of the latter lesions may occur and be very destructive. The papule is usually found on the palms, sole, buttocks and face, but it may be present in any part of the body. When located on the buttocks or sole, exfoliation is quite marked, and in cases where the papules are numerous and confluent some of the epidermis may fall off in round, large pieces. The skin underlying the confluent syphilid is of a copper color.

Vesicular Syphilid.—The vesicular syphilid is extremely rare and is usually associated with the papular or papular vesicular lesions. If the vesicles are large, the contents become purulent.

Pustular Syphilid.—Pustular syphilid may be observed at birth, but as a rule it follows the appearance of the papular syphilid. The lesions may not appear until relatively late after the initial eruption. It is most frequently seen in children whose general condition is much below par. The thighs, buttocks, face, scalp, groins and soles are most frequently involved. The lesions vary considerably in size. The pustule may disappear without leaving any permanent change, but pigmentation is usually observed for some time and scarring usually occurs. Occasionally, a child is born presenting lesions on the skin; these lesions are known as bullous syphilid or pemphigus syphiliticus. They are most frequently seen on the soles, palms, toes, fingers or limbs, and are especially likely to be present on a prematurely born infant. The blebs contain a cloudy serum, which soon becomes purulent. They are circular or oval in outline, but are sometimes irregular. They are surrounded by aureola and frequently become confluent. This type of syphilitic eruption indicates a marked intoxication. Sometimes the bullæ are distended, with a sanguineous fluid, and when they rupture hemorrhage results. The bleeding is slight, but indicates extreme poisoning. Such cases are usually fatal.

Tubercular and Gummatous Syphilids.—Tubercular and gummatous syphilids usually appear relatively late—usually within the second or third decade of life. As a rule, only a single group occurs; it may be dry or ulcerative in type and circular in outline. The face is the common site for the lesion, the area about the nose being especially predisposed, but the anterior surface of the leg is also a common site. The lesion develops insidiously; it is of a copper color and painless. When ulceration results it gradually spreads, or it may heal and be replaced by scar tissue.

Fissures and Mucous Patches.—Fissures constitute some of the most characteristic findings of early hereditary syphilis. They are most commonly seen in the region of the mouth and nose, but may occur in other places. They are multiple, deep, bleed readily, and are painful. They do not respond to local treatment, and scars result from healing of the ulcerations. The fissures are transverse to the border of the lips or anus, and the cicatrization causes a puckered appearance of the skin When the papule is located in a region which is constantly moist or where two surfaces come in contact, mucous patches commonly result. They are most frequently found on the lips, vulva, anus and scrotum, but may occur in other areas, such as the axillæ and the folds of the groins. The lesions are raised and vary in size from 3 to 12 millimeters and are of a grayish-white color. Ulceration of these lesions may occur.

Hair and Nails.—*Alopecia.*—Alopecia is a characteristic symptom of hereditary syphilis. It is frequently observed at the time of birth and varies in degree. Complete loss of hair is seldom observed. As a rule, the process consists of a general thinning of the hair. The eyebrows may also be affected. The hair which remains is scraggly and appears dry.

Onychia and Perionychia.—Affection of the nails is rather common in hereditary syphilis. Like in acquired syphilis, it is of different types. A single nail may be affected, but as a rule a number of them are involved or all of them may be affected. The nails become thickened, lose their color and become separated, or the nail breaks easily.

Bones and Joints.—*Bones.*—Involvement of the bones is very common in hereditary syphilis. The long bones, especially the tibia, and the bones of the head and nose, are most frequently involved. Syphilitic process usually shows itself as a periostitis or an ostitis, a gummatous invasion, or osteomyelitis. The syphilitic process is usually productive rather than destructive in nature and usually appears after the fifth year.

Periostitis is the most common lesion involving the bones in hereditary syphilis. Any of the skeleton bones may be involved, but the tibia is the most frequently affected. A tender, painful swelling occurs, which increases on motion. As a rule, thickening of the periosteum occurs, but necrosis may result. Necrosis is relatively rare, and deformity of the bone is more likely to occur. Gummatous invasion may lead to bone necrosis with the formation of a sinus. Such invasion generally affects the tibia, but invasion of the bones of the hands and feet is not uncommon. Hyperplasia of the long bones may occur, and most frequently involves the tibia. The bone may increase to twice its normal size as the result of periosteal thickening. The disease runs a chronic course and may be free from pain, and deformity of the bone results. This deformity as a rule is permanent. Lengthening of the bones is occasionally observed.

Syphilitic Dactylitis.—This is an early sign of hereditary syphilis which is occasionally present. The fingers are more frequently involved than the toes, and as a rule, more than the fingers is involved. The proximal phalanx is the more frequently affected. Swelling is marked; it may break down and discharge, and the color of the skin becomes purplish. The disease may affect the subcutaneous tissues or the tissues surround the bone. It may invade the bones or it may primarily affect the periosteum and extend to surrounding tissues. When the bone itself is involved, the condition is identical with osteomyelitis and may lead to much destruction of bone and joint tissue.

Exostoses.—Exostoses may occur on the cranial bones. They are oval in shape and elevated and most frequently located on the frontal and parietal bones. The lesions are usually symmetrical. The skull may appear of various types: (1) That of the rachitic skull, showing the characteristic softening in the squamous portion and along the sutures, similar to that observed in cranial tabes. (2) It may appear as an abnormal protuberance on the frontal and parietal bones. This usually occurs during the first months of life. (3) Periosteal swelling and rarefaction of the bone may occur in isolated areas; such a process is less common than that observed in other types of lesion. It shows itself as areas of caries, surrounded by walls of bone. Hydrocephalus may be caused by inflammation of the meninges and choroid plexus with or without obstruction of the aqueduct of Sylvius. The head becomes much 'enlarged in size, out of all proportion to the rest of the body.

Joints.—Hereditary syphilis of the joints is comparatively rare, since the majority of children affected with hereditary syphilis are stillborn or die within a short time after birth. However, syphilitic involvement resembling a simple synovitis may occur. It manifests itself as an effusion, which may be extensive and not be associated with cartilage destruction, or it may manifest itself as a synovitis which produces thickening of the synovial membrane.

When joint involvement occurs, it usually manifests itself as a syphilitic osteochondritis. Osteochondritis affects the diaphyseal end of the epiphysis. It may inhibit bone formation by destruction of the cartilage cells, or bone development may be delayed. The long bones, such as the humerus, radius, ulna, tibia and femur, are the most commonly affected, but other bones may be involved, such as the ribs, sternum and bones of the head and feet. Swelling becomes fairly pronounced and synovitis may result. Granulation tissue-formation may occur between the shaft and the epiphysis and produce separation. On section, the bone presents a yellow rugged line at the junction of the diaphysis and epiphysis. Arthritis, when present, may be either acute or subacute in type. Any of the joints may be involved, but the femur is the most frequently affected. Synovitis is the usual lesion and may make its appearance rapidly and be associated with much pain and tenderness. As a rule, but one joint is affected and the process responds well to treatment.

LIVER.—The liver is almost always involved in a child afflicted with hereditary syphilis and it may be the only symptom of a syphilitic infection. The liver becomes considerably enlarged and is hard and painful. The chief lesion is interstitial hepatitis, but gummatous hepatitis may also occur. Occasionally jaundice may result from obstruction of the bile passages. Ascites may be present and the abdomen distended.

SPLEEN.—Splenic enlargement is one of the earliest symptoms of hereditary syphilis. Enlargement is usually most marked in the late type, and especially following second dentition. Splenomegaly is usually associated with liver involvement. The pathological changes consist of an interstitial fibrosis, but gummata may be found.

PANCREAS.—In severe infections, the pancreas is especially likely to be involved. There is an infiltration of plasma cells, a slight proliferation of connective tissue, which appears edematous and replaces the parenchyma of the organ.

THYMUS.—Occasionally, the thymus is involved in this type of syphilis. The affection shows itself as a number of abscesses which contain purulent material. According to Oliver, syphilitic disease of the thymus manifests itself primarily as a degeneration of lymphocytes and Hassall's bodies, with an hypertrophy of the reticular epithelium and hyperregeneration of the concentric corpuscles. The abscesses known as Du Bois abscesses are very characteristic of syphilis.

KIDNEYS.—Inflammatory changes may occur in the kidney, leading to chronic nephritis, either parenchymatous or interstitial in type. Nephritis may be observed as early as 5 weeks after birth, but this is not common. Paroxysmal hemoglobinuria may occur, but it is a relatively late symptom and does not appear before the second year.

TESTES.—Testicular involvement is not common in hereditary syphilis. Orchitis is the most frequent infection and usually involves the body of the gland rather than the epididymis, and is usually bilateral. Involvement of the testes may occur as early as a few weeks following birth. When it occurs at this time it is of great diagnostic value.

RESPIRATORY SYSTEM.—Hereditary syphilis of the lung may be circumscribed and be gummatous in type, or it may be profuse and constitute what is known as white pneumonia or interstitial pneumonia. For the most part, the two processes are combined. Interstitial pneumonia is most commonly found in the lungs of children who die a short time after birth or who are stillborn. The lungs appear white or only slightly reddened and are practically free from air. A child afflicted with interstitial pneumonia lives but a short time. Unless a catarrhal condition is present there is little or no involvement of the larynx and the epiglottis becomes affected. Stenosis of the trachea or bronchæ is rarely observed, and is due to cicatrization of a gummatous mass. The nasal passages are the most frequently affected part of the respiratory system. The mucosa is chronically inflamed and may be followed by ulceration; or the nasal bones and cartilages may become eroded, and necrosis may result.

NERVOUS SYSTEM.—The symptoms produced by hereditary syphilis are very similar to those resulting from the acquired form of the disease. The lesions may be multiple and may appear early in life, or they may make their appearance relatively late in life. When late, they may appear around the age of puberty, but not necessarily so early. The meninges or the brain itself may be involved. When the brain is affected, the cause is primarily vascular. Syphilitic meningitis may consist of a simple hyperplasia of the meninges or it may be of a gummatous nature and the meninges be covered with miliary gummata. Like in the acquired type of the disease, the basilar area of the brain is the part most frequently affected by miliary gummata.

LYMPH GLANDS.—Lymphatic enlargement in hereditary syphilis is similar to that observed in acquired syphilis. Swelling of the lymph nodes occurs, which is multiple, not inflammatory, free from pain, and distinctly palpable. Ulceration rarely occurs.

EYES.—Interstitial keratitis is the most characteristic lesion affecting the eye in hereditary syphilis. It is most commonly observed between the ages of 6 and 20 years; it is rarely seen after 30 years of age, but may occur as early as 3 years. The affection usually begins in the center or at the margin of the cornea. The cornea becomes hazy as a result of the cellular infiltration of the corneal tissue itself. The haziness gradually becomes more diffuse. Ciliary congestion occurs and the patient complains of irritability and photophobia. The opacity produced is not uniform, but spots occur which are whiter than others. Interstitial keratitis constitutes one of the symptoms of Hutchinson's triad.

Acute iritis of the plastic type is rare in early hereditary syphilis, but may occur as early as the second to the fifteenth month. It makes its appearance after the skin eruption and is very important. Unless the condition is observed and proper treatment administered, the vision may be impaired. The pupil is more or less irregular, the iris appears dull and discolored, and an area of congestion may be noticed. Optic neuritis, retinitis and choroiditis are the lesions frequently observed.

EARS.—Hereditary syphilitic enlargement of the ear occurs during the first three decades of life. Affections of the outer and inner ear generally occur during the first few days, months or years of life, while labyrinthine involvement generally occurs during the second decade. Bullæ, macules and papules may occur on the auricle. The infection of the middle ear shows characteristics which differentiate it from ordinary otitis media. Syphilitic otitis media usually develops quite rapidly, in the first weeks or months after birth. It is painless, and the only symptom may be a purulent discharge. Unless treatment is rapidly administered, the process becomes chronic and leads to irreparable changes, such as bone involvement, deafness and mastoiditis. Labyrinthine disease is usually bilateral and results in total deafness. Mutism is the result of such involvement in early life. If labyrinthine involvement occurs late in life, the patient complains of tinnitus.

TEETH.—Changes produced in the first teeth may be due to other conditions than syphilis. Any pathological process which is sufficiently active to interfere with the development of the teeth may affect them in various ways. The enamel tissue may be wanting or imperfectly located on the teeth, or the mesodermal tissue may be involved and produce dentine, which is soft, easily eroded and subject to early delay. Systemic disturbances, diseases of the mouth and gums, as a result of gastro-intestinal disturbances, may produce changes in the permanent teeth. The teeth may be abnormal in shape, irregular in contour, rough, improperly placed, and appear unhealthy. If the syphilitic infection does not affect the teeth during their development, they will erupt and be normal in shape and structure. Since syphilitic stigmata are present at the time that the teeth are developing, they cause an interference in the process of calcification.

The degree of dental involvement is directly dependent upon the presence of an actual syphilitic process at the time of dentinification. If infection is very severe at the time that dentition is beginning, the teeth will be more extensively involved than if dentition is advanced. Dental stigmata are therefore of value in determining, to a certain degree, the time when infection of the fetus occurred. Syphilitic hypoplasia of the first teeth is rare, since dentition occurs at the 17th or 18th week of intra-uterine life and infection of the fetus at this time usually results in the death of the fetus. The teeth most commonly affected during the second dentition are the incisors, the first molars and the cuspid teeth. The first molars are undergoing dentinification during the last months of pregnancy, while the incisors and cuspids undergo dentinification about the third or fourth month after birth. Dentinification of the crowns of the incisor teeth is only partially complete for some months after birth, with the result that if syphilitic stigmata are present, about half of the crown is affected. Considerable dentinification is present in the first molars at about the fourth month, with the result that the crowns are less involved. As a rule, dental stigmata are symmetrical and hypoplasia is noticed on the same group of teeth, and the teeth are involved to about the same extent.

There are several stigmata which are especially characteristic of hereditary syphilis:

Hutchinson's Teeth.—This type of tooth is characterized by crescentic indentification of the free edge of the tooth. The superior central incisors of second dentition are most commonly affected, but the four inferior incisors or even the cuspid teeth may be involved. The teeth are broader at their neck than at their free edge (peg-shape tooth). The angles are rounded and the inferior and lateral borders more or less merge by a curved line. Convergence of the teeth is observed.

The typical Hutchinson's tooth is very pathognomonic of syphilis. Its individuality is such that it can hardly be considered as the result of any other disease than hereditary syphilis. The characteristics vary, however, with the age of the syphilitic infection. When the tooth first makes its appearance, the characteristic semilunar shape is absent. Hypoplastic tissue fills the areas, which is later replaced by the crescent. This hypoplastic tissue is free from enamel, is friable, breaks easily, and soon gives rise to the characteristic crescent shape. The tooth is also beveled from before backward and downward. Later, in the young and adolescent, the surface of the tooth changes, and by the 25th year the characteristic stigmata are almost entirely absent. The semilunar outline has disappeared but the beveling persists until about the 30th year, when the tooth is shorter and has lost the characteristics of the Hutchinson's tooth.

Other Types of Hypoplasia Affecting the Incisors.—(*a*) *Flattened Surfaces.*—The free surfaces of the teeth become flattened and appear abnormal in color, varying from yellow or gray to almost a black shade. The surface is irregular, rough and furrowed.

(*b*) *Saw Tooth.*—The surface is irregular, rugged, and presents the appearance of furrows produced with a file.

Hypoplasia of the Fourth Permanent First Molar Teeth.—The shape of the tooth is markedly changed. In early life, about three-fourths of the free surface is hypoplastic. The hypoplastic portion of the tooth is diminished in size, eroded, and marked off from the rest of the teeth by circular constriction. The tooth presents the appearance of a stump. It is rough, pointed, fissured, and is of a brownish or black color.

The presence of such teeth is of great diagnostic value in the diagnosis of syphilis.

Delayed Dentition and Microdentism.—These conditions are stigmata of hereditary syphilis. As a rule, delayed dentition relates to all the teeth, but certain groups, such as the incisors, may alone be affected. The condition may affect the permanent teeth as well as the deciduous teeth. Microdentism is rare, and usually affects the superior and inferior lateral incisors.

Persistence of Deciduous Teeth.—Failure of the permanent teeth to replace the first teeth may occur. Such a condition is suggestive of hereditary syphilis. The deciduous teeth may persist, as the result of failure of the permanent teeth to develop and thus replace the latter.

Amorphism.—This condition is not at all infrequent in hereditary syphilis. The teeth may be of various abnormal types or they may vary slightly from the normal. They are very vulnerable and caries develop rapidly. The teeth may be improperly placed or some of them may be entirely absent. The superior central incisors may be small and very narrow at their free surface. The surface is rounded and the convex surface extends upward. There is a convergence of the teeth. The presence of such teeth is indicative of hereditary syphilis.

Diagnosis of Early Hereditary Syphilis.—The diagnosis of hereditary syphilis depends, to a considerable degree, upon the history of the parents. It is necessary to ascertain from the parents whether either one or both has ever been infected and how much time has elapsed since the infection. If the infection is relatively recent, in relation to conception, the transmission to the fetus is much more likely. The history should include a record of any abortions or miscarriages on the part of the mother. This is especially important if they have been frequent or if any children have died a short time after birth. The syphilitic fetus is frequently born prematurely. History of premature births is of diagnostic value. The condition of the premature child at the time of birth should be noted, as regards its development, the condition of the skin and mucous membrane, or any other condition which may be suggestive of syphilis. Symptoms may be entirely absent at birth, but present themselves within a few weeks. Coryza, commonly known as "snuffles," hoarseness, cutaneous lesions, splenic or hepatic enlargement, malnutrition, pseudo-paralysis or simple inflammation at the diaphyseal-epiphyseal junction of the bones are the symptoms commonly looked for.

The diagnosis postmortem of hereditary syphilis in a stillborn child, or one who dies soon after birth, is made by a careful examination of the epiphyseal lines for osteochondritis, while pneumonia, splenic or hepatic enlargement, characteristic lesions of the skin or the mucous membranes—such as macules, papules or pustules, or syphilitic pemphigus—are of great value in making a diagnosis of hereditary syphilis.

Diagnosis of Late Hereditary Syphilis.—The diagnosis of late hereditary syphilis depends upon the history of the parents and the history of former births, but there are more symptoms present at this time which are indicative of syphilis. The physical condition of the child is generally poor. He is poorly developed, feeble, and presents a senile appearance. His hair is dry, thinned, and the fingernails are brittle. The parietal and temporal bones may be specially prominent and the nose may be sunken, as a result of involvement of the bones and cartilages. Deformities and involvement of the long bones may be observed. Periosteal nodes may be present and scattered over the long bones or on the cranium. The presence of scars resembling purse strings about the mouth are highly suggestive of hereditary syphilis.

Hutchinson's triad is of great diagnostic value. It consists of the presence of characteristically deformed teeth, Hutchinson's tooth, interstitial keratitis and sudden deafness, which appears without subjective symptoms. These findings, taken in conjunction with the mental condition of the patient, the history of retarded growth, alopecia or paralysis, are sufficient evidence for making a diagnosis of syphilis. However, the presence of a positive Wassermann reaction definitely settles the diagnosis. Craig reports 82.2 per cent. positive Wassermann reactions in 22 cases, while Noguchi reports 100 per cent. positive and Vedder 96 per cent. positive Wassermann tests in congenital syphilis.

Treatment of Hereditary Syphilis.—The prophylactic treatment of congenital syphilis has been thoroughly discussed in the Treatment of

Syphilis during Pregnancy (p. 413), so it may well be passed over in these paragraphs.

In treating congenital syphilis, as in treating the acquired type of the disease, the **lesions should be cleared up** as soon as possible; and to this end the **same drugs should be employed** as are used in the treatment of acquired syphilis, namely, the **salts of mercury,** the **arsenic compounds** and the **iodids.** The chief difference in treating the two types of the disease consists in the size of the dose administered and probably also in the method of administering the drugs. The administration of the various drugs for the cure is, however, insufficient unless the **general condition of the child** is looked after. As a rule, hereditary syphilis is manifested by symptoms quite early—within the first month or so. We well know that during this period the **nourishment of the child** is the big factor to be considered, even in a healthy child, and in congenital syphilis it is a still more important feature.

The child should, above all, be **nursed at the breast.** If, however, there are contra-indications to nursing, or the mother is unable to nurse the child for any reason, it is very essential to secure a wetnurse. This nurse should be syphilitic herself; if the latter is not syphilitic, the milk must be removed from her breasts mechanically and fed to the child by bottle. Ernst Welde, of Berlin Charité Hospital, observed that with treatment, 42 per cent. of the artificially fed infants died, while the mortality of those who had proper treatment, and in addition were breast-fed, was less than half of that (20 per cent.).

When the mother has been intensively treated during her pregnancy there is a chance of obtaining a normal child. While the prognosis of congenital syphilis is none too favorable, the outlook is not nearly as gloomy, at that, as some would lead us to believe. Finkelstein states that the unfavorable opinion generally held with regard to the fate of congenitally syphilitic infants and children is in no way confirmed by statistics or observation. Although the children may not be extraordinary, yet they may grow up and be quite robust. He states, moreover, that the number of weaklings and anemics is no greater than among a similar group of children free from syphilitic ancestry.

The *time at which the mother contracted the infection* influences the infection of the fetus, and Bertha Sabin, after some study of the question, decided that where the mother has syphilis at the time of conception or before the fifth month of pregnancy the child is nearly always syphilitic.

Wechselmann administers the **neosalvarsan into the region just above the gluteal fascia,** and with very good results. The needle is inserted and moved in a pendulum manner back and forth. If it is just over the fascia, a scratching, grating sensation is either felt or heard as the point of the needle scrapes over the fascia. Then the needle is rotated along its long axis, in order to be sure that it is quite free and not entangled. Next, 1 c.c. of sterile salt solution is injected in a syringe, and the barrel of the syringe removed. If the needle is next to the fascia, the water will regurgitate through the needle. The **neosalvarsan** is then injected.

As to the *dose of neosalvarsan* which is to be used, there is no fixed rule; it varies with the age and weight of the child. Lesser, of San Francisco, Cal., believes that 0.015 gram to every kilo of weight (2½ lbs.) is a safe average for the initial dose. The **dose of salvarsan** is somewhat less, about .01 gram per kilo. The dose is gradually increased to .20 or .30 gram per injection.

Mercury produces very good results when used **in conjunction with the neosalvarsan.** It is usually used **by the inunction method or by ingestion.** When used by inunction, it should be rubbed in very lightly, since the child's skin is very easily irritated. Since the skin on the bottom of the feet is thicker, it may be rubbed on the soles of the feet, or the ointment may be applied to the belly-band and thus allowed to absorb. *Dose:* 1 gram per 10 kilos of body weight.

Mercurial baths at one time were much used, but to-day their use is not much in vogue, as the danger of dermatitis is great and the exact amount absorbed is uncertain. *For very small children,* from 5 to 10 grains of **bichlorid,** with an equal amount of **ammonium chlorid,** is added to about 5 gallons of water and the child bathed for 10 to 15 minutes. This bath should be administered every day or every other day.

When administered **by ingestion,** the **gray powder,** consisting of mercury and chalk (¼ to ½ grain), or **calomel** (1/20 to 1/10 grain) three times daily, are the drugs most commonly used. The administration of the drugs in this way has the drawback of irritating the stomach at times and leading to gastro-intestinal symptoms. **Mercury** may also be administered **by injection,** and this is the method often prescribed in treating nurslings, since their skin is usually so very delicate. However, **inunction and injection may be alternated.**

Rectal administration is ideal for these babies, as a **suppository** can be slipped into the rectum with little trouble. Its therapeutic effects administered in this way are excellent and the local irritation is nominal.

Iodids are also of value, since they aid the elimination and absorption of the toxic material. The iodids are usually administered in the form of a saturated solution. An initial dose of 2 to 3 grains is advised and the dose rapidly increased to 5 or 10 grains three times daily.

Sylvester reports a comparative study of cases of congenital syphilis, some of which were treated by mercury alone and some of which were treated with mercury in conjunction with neosalvarsan. Of the early type treated at the Children's Hospital of Boston, mostly under six years, 18 presented clinical evidence of early syphilis with positive Wassermann reactions, but did not seem acutely sick. These received mercury alone; none died; all did fairly well, and were clinically free from signs of syphilis in from 2 to 6 months, but only 2 had negative Wassermann reactions. These cases were treated over a period of one and one-half years. Of the other cases under observation, 9 were treated with **"606" and mercury.** The effects were rapid: 7 treated for nearly two years have had 2 negative Wassermann tests three months apart. Moreover, in treating 16 cases of very sick infants with salvarsan and mercury, only 4 died, 2 did not return to the hospital, and 2 developed bronchopneumonia. Of 20 consecutive cases admitted to the hospital before the advent of arsenic, 16 died, 1 is living, and 3 cannot be found. We see from these statistics that the **combined arsenic and mercurial therapy** produces the best results and also that **intensive treatment is necessary** before a negative Wassermann reaction may be obtained, which is the best indication to a cure.

The hope of effecting a cure in a nursing child by the **antisyphilitic treatment of the mother** needs little more than comment. Numerous experiments have been performed to establish the presence of the drugs in the milk, but with little or no results. It would therefore seem that the benefit which the child sometimes derives is due to the passage of antitoxins from the mother to the child in the substance of the milk (Dukot).

In treating congenital syphilis it is of extreme importance to **consider the host primarily and the spirochete secondarily.** All the rules laid down for the protection of the host from large amounts of toxic dead spirochetic material should be carefully observed in treating syphilitic babies.

DISTRIBUTION AND HISTORICAL SUMMARY

The time at which syphilis first made its appearance has been a much debated question for a number of years. There are those who consider it pre-Columbian in origin, insofar as its appearance in the Old World was concerned. The occidental and oriental literatures contain much evidence of the existence of venereal disease at very early times, but there is not a single document which describes a disease in such a manner that it can be identified as a syphilitic infection.

Appearance of Syphilis in Europe.—It was toward the end of the fifteenth century that syphilis first made its appearance in the Old World. It appeared as a great epidemic which spread rapidly and affected people of all races and classes.

In 1494, Charles VIII, of France, invaded Italy for the purpose of conquering Naples, with an army composed largely of mercenaries, gathered from all parts of Western Europe. Because of the weakness of the Italian State, Charles was successful in his enterprise and took Naples with little difficulty. However, he was soon forced to relinquish his conquest because his army had become greatly weakened, as the result of a venereal disease which was affecting his troops. The epidemic spread very rapidly and pursued a very malignant course, such as disease pursues when it first makes its appearance in a virgin country where the people as yet have developed no trace of immunity toward it.

By 1495, it had already penetrated the most northern part of the Alpine peninsula and extended to the borders of France, Switzerland and Germany. Such a disease was never before known in Italy and, as a result, it was considered that it was introduced from some other country. The Italians considered that the French soldiers were responsible for its introduction and called it "the French disease," while the French believed that the soldiers contracted it in Italy, and named it "the Italian disease." Whenever the affliction made its appearance in another country, the disease was named after the people from whom the infection was supposed to have been obtained. The English and Turks called it "the French disease"; the Russians called it "the Polish disease"; the Hindoos and Japanese called it "the Portuguese disease." The Spaniards considered it as having been introduced from the New World, and called it "the disease of the Espanola Isle," known by the Indians as Haiti.

Soon after the disease spread to the various countries, laws were enacted to prevent the further spread of so severe a plague. The afflicted person ran a high fever, had severe bone aches and headaches, skin eruptions, and suffered with great prostration. By 1495, syphilis was prevalent in France, Switzerland and Germany; by 1497 it had reached England and Scotland, and by 1499 Russia and Hungary were invaded. The Parisian Parliament ordered all persons afflicted with the disease to leave the city within twenty-four hours; the Council of Aberdeen, Scotland, ordered all prostitutes to desist from their vice and work for a living. Failure to obey caused them to be branded on the cheek with a hot iron and banished from the town. The English Privy Council later passed an edict ordering all afflicted persons to be banished to the Island of Inchkeith, near Leith.

Appearance of Syphilis in the Orient.—Later, the disease made its appearance in the Orient. The researches of Okamaura and Sasuki for Japan and China, and Jolly and others for India, showed that syphilis did not exist in these countries until it was introduced from Europe. It made its appearance in Nagasaki, Japan, as early as 1569, after a visit of Europeans.

Origin of Syphilis in America.—The severity of the epidemic in the Old World would indicate that such a disease was new to that country and that it did not exist as a less malignant type up to that time. Since the most recent communication with the outside world was with the West Indies, it was only natural to suppose that the disease was introduced from that locality. Syphilis was considered as a disease new to Europe and the Orient; it had no name, and its spread was directly related to the invasion of Italy by Charles VIII and the scattering of his army following the invasion. The European and oriental bones of pre-Columbian times have been carefully and extensively studied to detect any syphilitic changes which might be present. The finding of syphilitic changes in the bones would furnish conclusive evidence of the existence of the disease before the appearance of the epidemic. Numerous collections of pre-Columbian bones were carefully studied by Virchow, the eminent anthropologist and pathologist, but in no case was he able to find lesions which indicated syphilis. The study of the bones collected from various parts of North America, Central America and

South America revealed the presence of syphilitic lesions, but it is difficult to definitely determine whether these bones which were studied are truly pre-Columbian, since there is no particular difference in the graves of the two periods. The same methods of burial and the forms of graves survived for centuries after the discovery of America. The writings of various men furnish the best evidence indicating the existence of syphilis in America before the arrival of Columbus.

Historical Summary.—In 1895, Seler called attention to the work of Montejoy Rabledo, a Spanish Army Surgeon, who had carefully investigated the origin of syphilis. His information was obtained almost exclusively from Spanish authors and his work was carefully and critically done. His findings were reported at the Fourth Meeting of the Congresso Internacional de Americanistas, held at Madrid, in 1882. Montejo reviewed the work of Diaz de Isla, Olviedo, Las Casas and other writers, but the work of Diaz de Isla is the most important evidence supporting the recent origin of syphilis of the Old World.

Diaz de Isla was a physician of some note, who himself witnessed the invasion of the disease. He was a surgeon at the Hospital of All Saints in Lisbon for ten years and had a large experience in syphilis. In a book written by him, and published between 1510 and 1520, he gives an account of his experience with the disease. He states that syphilis was unknown in Europe before 1493 and that, as far as Europe was concerned, it had not made its appearance until Columbus's crew brought it to them from the Isle of Espanola. He also states that the majority of Columbus's crew returned to Spain infected with the disease, which they had acquired in Haiti, and that he himself treated several of the syphilitic sailors, including the pilot, Pinzon de Palos, and that after the arrival of Columbus in Barcelona in 1493, syphilis spread among the inhabitants. Moreover, he states that at the time of Columbus's arrival in the West Indies, the Indians already possessed a highly complicated, rationally developed and deduced method of cure for the ailment, consisting chiefly of guaiacum and other vegetable beverages in conjunction with hydrotherapeutics, dietetics and climatic methods of treatment. His statements are confirmed by Olviedo, and Las Casas, both of whom visited America a few years following the discovery of America. Olviedo states the disease was contracted by the soldiers from the Indian women and spread by them on their return to Spain. In a report to Emperor Charles V, he states that it is certain syphilis originated in the West Indies, but was of a milder type than in Europe. Las Casas confirms the existence of syphilis in the New World at the time of discovery and maintains it is certain that the disease was either carried to Spain by the Indians who accompanied Columbus, and whom he himself saw at Seville, or by the Spaniards who became infected while in the West Indies.

Up to the time of Ricord, in the early part of the nineteenth century, the three venereal diseases—syphilis, chancroid and gonorrhea—were not clearly differentiated and were thought to be fundamentally the same disease. Ricord, moreover, recognized three stages: The primary stage began with the chancre, was auto-inoculable, and the induration of which expressed the passage of the poison into the tissues. The second stage—the syphilis—he considered non-contagious but transmissible to the offspring. The third stage, with involvement of the bones and viscera, he considered non-transmissible. It was not until 1859, when the contagiousness of secondary syphilis was established, and particularly within recent years, that tertiary lesions have been shown to be contagious.

Ricord, by performing 2,500 inoculations, proved that gonorrheal secretions would not produce syphilis, thus disproving John Hunter's conclusion that secretion from a case of gonorrhea was capable of producing both the chancroid and syphilis, and that the virus of the three diseases was therefore identical.

Hereditary syphilis was first scientifically recognized when the existence of delayed syphilis was proved by Stoll, Plenck and Rosen von Rosenstein.

In 1903, Metchnikoff and Roux successfully inoculated monkeys with syphilitic virus, and in 1905 Schaudinn discovered the *Treponema pallidum* as the specific organism.

SOCIOLOGICAL ASPECTS OF THE DISEASE

Syphilis and Marriage.—The relation which syphilis bears to marriage is very important and merits considerable attention, under the following heads:

(1) Syphilis acquired before marriage: (*a*) husband, (*b*) wife.
(2) Syphilis acquired after marriage: (*a*) husband, (*b*) wife.

1. Syphilis Acquired before Marriage.—The questions which present themselves for solution are: Is the danger of infectiousness past in both these groups? Is the danger of transmission to offspring past? Are there any sequelæ present that would render the individual sterile or impotent?

There are several factors which determine the prognosis of syphilis as regards marriage. They have been quite well formulated by Fournier, who says that marriage may be contracted:

1. If all active lesions are absent, such as the primary sore, mucous patches or roseola.
2. If the disease is in an advanced stage. It is well known that syphilis is not very readily contracted after it has run a course covering several years and all the infectious lesions have healed.
3. If a period of immunity has been present after the last signs of the disease have disappeared.
4. If the quality of the disease has not been severe. A patient whose case runs a very severe course should not be allowed to marry

unless the progress of the disease has been definitely checked and a cure obtained.

5. If prolonged treatment has been employed, this treatment having been intensive and sufficient.

All of these conditions must be satisfied before the patient is allowed to marry; if any one of them is not satisfied marriage should not be allowed. Fournier later became an extremist and instead of allowing marriage at the end of 5 years, he required that the patient be free of symptoms for 6 or 7 years. Authorities are quite generally agreed, however, that from 3 to 5 years is a sufficient period of time to elapse, after which time the patient may be allowed to marry.

Keyes says that the marriage of a syphilitic is often safe and sometimes justifiable at the end of 3 years, but that it is more prudent to permit marriage only after 5 years, during the last 2 of which the patient has been free from symptoms and without treatment. Gougerot, who is one of the latest writers on the subject, says marriage is permissible in the male 4 years after the infection, provided the patient has been free from symptoms for some time. He requires 8 years for the female. Lesser also believed in a longer period of observation in the female, since he realized the possibility of the *Treponemata pallida* remaining in the ova for a longer time than in the seminal fluid, his explanation of the fact being that the ova formed in the average at an early period of life, while the seminal fluid was produced as needed.

Gougerot, moreover, requires a negative seroreaction and insists that the patient be free from any nervous lesions. He also performs lumbar puncture and states that the spinal fluid should be negative. Fournier in a selection of 84 cases showed that 74 cases of nervous involvement occurred after benign syphilis. This shows the necessity for early, intensive treatment and discretion on the part of the physician when he makes the prognosis as to marriage. He must not lose sight of the fact that the general physical condition is almost as important as a negative Wassermann. A double syphilitic orchitis may be a contra-indication to marriage, because of sterility produced by it. If any question exists as to this, a specimen of semen should be obtained and examined first as to the presence of spermatozoa and, second, as to their vital strength and probable ability to fecundate.

The following are the author's present rules as a basis for advice to a syphilitic about to marry:

1. At least three years must have elapsed since the acquirement of the infection in a man and five in a woman.
2. They must have had two years, at least, of treatment: mercury or salvarsan.
3. They must have been free from all infectious lesions for at least one year; better, two.
4. Blood-serum should be negative.
5. Spinal fluid should be negative, but this is not absolute, as

we know that many individuals with positive spinal fluids beget healthy children and do not infect their marriage partners.

6. The longer the interval after the infection, the better the chance of healthy offspring.
7. When the wife becomes pregnant, she should be treated as outlined under Syphilis and Pregnancy (p. 413).
8. The prognosis when the wife is syphilitic is less favorable than when the husband is infected. When both are infected, the prognosis is very bad and a long time must be allowed to elapse —eight to ten years.

2. Syphilis Acquired after Marriage.—When syphilis has been acquired after marriage, the danger of infecting the marriage partner is very great. As soon as the infection is discovered, intensive treatment should be begun. The parties are to refrain from all intimacies until the infectiousness of the affected person is past. Impregnation should be prevented until cure is obtained and the birth of a healthy child quite certain. The relation of syphilis to pregnancy has been discussed in other paragraphs. Suffice it to say that treatment should be administered during the pregnancy to avoid any recurrence of the disease.

Exceptions for social causes and marriages of convenience are permissible in the fourth and fifth year, and particularly when both parties are infected.

BIBLIOGRAPHY

Etiology

Aratsu and Noguchi. Jour. Exper. Med., March, 1917, xxv, 349.
Bandi and Simmonville. Centralbl. f. Bakteriol., 1905, xl, 64.
Grossman. Jour. Am. Med. Assn., lxviii, 963.
Hazen. Med. and Surg., Oct., 1917, i, 875.
Heimann. Jour. Cutan. Dis., xxxiv, 653.
Kendall. Bacteriology—general, pathological and intestinal.
Levaditi and Petresco. Presse méd., 1905, xiii, 617.
Matzenauer. Die Vererbung der Syphilis.
McIntosh. Military Surg., xxxii, 184.
Metchnikoff. The new hygiene.
Montgomery. Jour. Cutan. Dis., xxiii, 145.
Noguchi. Am. Jour. Syph., Apr., 1917, i, 261.
——— Jour. Exper. Med., Mar., 1917, xxv, 349.
Schamberg. Jour. Am. Med. Assn., lvii, 783.
Wile and de Kruif. *Ibid.*, lxvi, 646.
Zinsser, Hopkins and McBurney. Jour. Exper. Med., xxiii, 329.

Symptoms and Physical Findings

Brooks. New York State Jour. Med., Apr., 1916, xvi, 185.
——— Med. Clin. North Amer., Nov., 1917, i, 605.
Buschke and Zernick. Arch. f. Derm. u. Syph., 1910, cvi, 121.
Carr. Illinois Med. Jour., Mar., 1918, xxxiii, 149.
Church. Nervous and mental diseases.

CLARK. Jour. Am. Med. Assn., lxvi, 1665.
CORBUS. Modern urology, Cabot, Vol. II, p. 177.
DOWNEY. Am. Jour. Syph., 1917, i, 616.
EDWARDS. Principles and practice of medicine, 1916, p. 204, 207.
EINHORN. Med. Rec., New York, Mar. 13, 1915, lxxxvii, 421.
EUSTERMAN. Am. Jour. Syph., 1918, ii, 205.
FOURNIER AND SABAREANU. Bull. Soc. Derm. et Syph., 1900, xi, 167.
FUCHS. A textbook of ophthalmology. Translated and revised by Duane.
GAUCHER. Bull. l'Acad. de méd., Paris, Oct. 2, 1917, lxxviii, 349.
——— Ann. de mal vén., Paris, xi, 326.
——— Bull. Acad. de méd., Paris, 1916, lxxv, 610.
GOUGEROT. Traitment de la syphilis en clientelle.
GROSSMAN. München. med. Wchnschr., xliv, 473.
HALLOPEAU AND FOUQUET. Traitment de la syphilis, 1911.
HARTZEL. Diseases of the skin.
KEYES. Syphilis.
LEVISON. Am. Jour. Syph., Jan., 1918, ii, 45.
MACKENZIE. Diseases of the heart. 3d Ed., p. 270.
MARSHALL. Syphilology and venereal diseases, 1914.
MEYERS. New York State Jour. Med., xii, 531.
MORGAN. Am. Jour. Med. Sc., Mar., 1915, n. s., cxlix, 392.
MORTIMER. Am. Jour. Syph., St. Louis, Apr., 1917, i, 473.
MUBLMAN. Deutsch. med. Wchnschr., June 15, 1917, cli, 733.
O'REILLY. Am. Jour. Orthop., 1914, xi, 431.
OSLER AND MCCRAE. Modern medicine. Vol. III, p. 446.
POWER AND MURPHY. A system of syphilis.
ROSENFELD. Berl. klin. Wchnschr., xxxix, 307-310.
STILWAGON. Diseases of the skin.
THIEBIERGE. La syphilis et l'armée.
THOMPSON. Am. Jour. Syph., 1917, i, 179.
VANDERHOOF. South. Med. Jour., Feb., 1917, x, 100.
WILE AND ELLIOTT. Am. Jour. Med., 1915, cl, 512.

Laboratory Findings

BLAINE. Illinois Med. Jour., Aug., 1917, xxxii, 100.
CRAIG. The Wassermann test, 1918.
DELAFIELD AND PRUDDEN. Textbook of pathology, p. 270.
DENNIE AND SMITH. Am. Jour. Syph., Jan., 1918, ii, 101.
FORDYCE. Am. Jour. Med. Sc., Oct., 1916.
GRADWOHL. Jour. Am. Med. Assn., Feb. 17, 1917, lxviii, 514.
HEIDINGSFELD. New York Med. Jour., Apr., 1916, cvii, 673.
KENDALL. Bacteriology.
KOLMER. Jour. Immunol., Dec., 1916, ii, 23.
NOGUCHI. The serum diagnosis of syphilis. 2d Ed., p. 158.
NONNE. Syphilis and the nervous system. 1913, p. 341. Translated by Ball.
STENGEL AND FOX. A textbook of pathology, p. 336.

Provocative Wassermann

BOAS. Die Wassermann reaction.
CRAIG. The Wassermann test.
GENNERICH. Berl. klin. Wchnschr., Sept. 19, 1910, cccclxxii, No. 38, 1735.
HERKHEIMER. Deutsch. med. Wchnschr., Aug. 10, 1910, ccclxii, No. 33, 1517.
KING. Jour. Am. Med. Assn., lxii, 1669.
LEREDDE. Le traitment de la syphilis. 1917, p. 31.
MICHAELIS. Berl. klin. Wchnschr., Sept. 12, 1910, cccclxxii, No. 37, 1695.
MILIAN. Dermat. Gesellsch., Dec. 1, 1910.

PEASE. Med. Rec., New York, 1914, lxxxv, 982.
REASONER. New York State Jour. Med., Jan., 1916, xvi, 4.
STOKES AND O'LEARY. Am. Jour. Syph., July, 1917, i, 629.
THOMPSON. Diagnosis and treatment of syphilis, 1916.

Special Examination

BLAINE. Illinois Med. Jour., Aug., 1917, xxxii, 100-104.
CARMAN. Am. Jour. Syph., 1918, ii, 297.
CHIEFFI. Gior. ital. d. mal. ven., May 26, 1918, lix, 65.
CORBUS. Syphilis of the genito-urinary organs. Modern urology, Cabot, Vol. I, p. 161.
EISLER AND KENZFUCHS. Deutsch. med. Wchnschr., 1913, xxxix, 2145-2146.
FLETCHER. Lancet, Oct. 21, 1916, ii, 710.
HAHN. Knochen Syphilis im Röntgenbild.
KEINBOCK AND HOCHSINGER. Arch. f. Dermat. u. Syph., 1901, lvii, 573.
KOLMER. Jour. Am. Med. Assn., lxvi, 1435.
LYONS. South. Med. Jour., June, 1916, ix, 489.
MARSHALL. Syphilology and venereal diseases, 1914.
MILLER. New York State Jour. Med., xv, 378.
SHERRICK. Jour. Am. Med. Assn., July 31, 1915, lxv, 404.
STILLIANS. Interstate Med. Jour., June, 1917, xxiv, 589.
STOKES. Jour. Am. Med. Assn., Apr. 14, 1917, lxviii, 1092.
THIEBIERGE. La syphilis et l'armée.
THOMAS. Lancet, Apr. 1, 1916, xxxvi, 198.
THOMPSON. Syphilis: diagnosis and treatment, 1916.
TZANCH AND BERNARD. Prog. Med., xxxii, 274.
WARE. Ann. Surg., 1907, 199.
WILE. Jour. Am. Med. Assn., 1913, lxiv, 1465.

Diagnosis, Complications, and Association With Other Diseases

ABBOTT. Lancet, Feb. 16, 1918, i, 269; Feb. 23, 1918, i, 307.
ANDERSON. Med. Jour. Australia, Mar. 30, 1918, i, 251.
BEESON. Arch. Diagnosis, Oct., 1917, 339.
GOODMAN. Am. Jour. Syph., Apr., 1918, ii, 344.
GOTTHEIL. New York State Jour. Med., Apr., 1918, xviii, 155.
HALLOPEAU AND FOUQUET. Traité de la syphilis, 1911.
LEREDDE. Traitment de la syphilis. 1917, p. 144.
——— A manual of venereal diseases. 2d Ed. Oxford Med. Public.

Physiological Action of Mercury and the Treatment of Mercurial Intoxication

BASTIDO. Modern medical pharmacology and therapeutics, 1918.
FANTUS AND HYATT. Jour. Lab. and Clin. Med., Aug., 1917, ii, 83, 813.
MEYERS AND GOTTLIEB. Pharmacology: Clinical and experimental. Halsey, 1914.
SOLLMAN. A manual of pharmacology, 1917.

Treatment of Syphilis Complicated by Pregnancy

BARTHOLOMEW. Jour. Mich. Med. Soc., 1915, xiv, 325.
CONS. Lyon Méd., Jan., 1917, 14; Feb., 1917, 63.
FINDLAY. Glasgow Med. Jour., Feb., 1918, lxxxix, 65.
FOURNIER. Le traitment de la syphilis.
LEREDDE. Le traitment de la syphilis.
LOSSEE. Bull. Lying-In Hosp., New York, June, 1916, ccxliii.

Prognosis

Bruhns. Berl. klin. Wchnschr., 1915, lii, 1057.
Hallopeau and Fouquet. Traité de la syphilis.
Keyes. Urology, 1917.
Leredde. Traitment de la syphilis.

Pathology

Allbutt and Rolleston. System of medicine, Vol. IV, pt. 20, p. 29.
Church and Peterson. Nervous and mental diseases.
Corbus. Modern urology, Cabot.
Fordyce. New York State Jour. Med., xv, 417.
Fuchs. Textbook of ophthalmology. Translated by Duane, 1917.
Gardner. Med. Times, New York, xliv, 141.
Gellhorn and Ehrenfest. Am. Jour. Obst., lxxiii, 924.
Gougerot. Traitment de la syphilis en clientelle.
Hallopeau and Fouquet. Traité de la syphilis.
Herxheimer. Ergebn. d. allg. Path. u. path. Anat., 1907, cxii, 589.
McNeil. Interstate Med. Jour., July, 1917, xxiv, 685.
——— Am. Jour. Syph., Oct., 1917, i, 738.
Morris. *Ibid.*, Apr., 1918, ii, 231.
Osler and McCrae. Modern medicine. Vol. IV, p. 804.
Schwartz. Am. Jour. Obst., lxxvii, 900.
Symmers. Jour. Am. Med. Assn., lxvi, 1457.
Warthin. Am. Jour. Syph., July, 1918, ii, 440.

Historical Summary

Powers and Murphy. A system of syphilis, Vol. I, pp. 1-36.
Pusey. Jour. Am. Med. Assn., lxiv, 1961.
Schoenrich. Urol. and Cutan. Rev., xix, 381.

Hereditary Syphilis

Chapin. Am. Jour. Obst., lxiii, 339.
De Schweinitz. Diseases of the eye. 8th Ed.
Fournier. Syphilis hereditaria tardia.
Gaucher. Bull. Acad. de méd. 3^e^ s., lxxvii, 437.
Hallopeau and Fouquet. Traité de la syphilis, 1911.
Heimann. New York Med. Jour., Sept. 23, 1916, civ, 592.
Helmholtz. Am. Jour. Dis. Child., x, 194.
Hoffman. Dermat. Ztschr., 1914, 508.
Holt. Diseases of children.
Jeans. Am. Jour. Dis. Child., xii, 374.
Lisser. California State Jour. Med., 1915, xiii, 469-474.
Morris. Med. and Surg., i, 949.
Oliver. Am. Jour. Dis. Child., xiii, 158.
Ostman. Lehrbuch der Ohrenheilkunde.
Pfæindler and Schlasmann. The diseases of children.
Post. Am. Jour. Dis. Child., xii, 364.
Powers and Murphy. A system of syphilis.
Stein. Med. Rec., New York, xc, 445.
Sylvester. Am. Jour. Dis. Child., xii, 395.
Vance. Kentucky Med. Jour., xiv, 583.
Wall. Arch. Pediat., xxxiv, 765.
Warthin. Am. Jour. Syph., 1918, ii, 433.

Wise. New York Med. Jour., Aug. 12, 1916, civ, 293.
Young. Med. and Surg., i, 836.

Syphilis and Marriage

Fournier. Syphilis et marriage.
Gougerot. Traitment de la syphilis en clientelle, 1914.
Keyes. Urology, 1917.
Leredde. Le traitment de la syphilis.
Lesser. Therap. Monatsch., 1896, x, 431.
Marshall. Edinburgh Med. Jour., 1903, n.s. 14, lvi, 146.
Muller. Würz. Abhandl. a. d. Gesamtgeb. d. prakt. Med., ix, 185.

CHAPTER XVII

GONOCOCCAL INFECTIONS

By David Geiringer, M.D.

and

Jorge Campuzano, M.D.

History of gonorrhea, p. 451—Prevalence of gonorrhea, p. 452—Duration of gonorrhea, p. 452—Etiology, p. 453—Bacteriology, p. 453—Pathology of gonococcal infection, p. 460.

Gonorrhea in the male, p. 462—Symptomatology of gonorrhea in the male, p. 463—Diagnosis of gonorrheal infection, p. 468—Treatment of acute gonococcal urethritis, p. 476—Internal remedies, p. 476—Local treatment of urethritis, p. 479—Routine treatment of acute gonorrheal urethritis, p. 484—Prophylaxis, p. 489—Abortive treatment, p. 489—Treatment of chronic gonorrhea in the male, p. 490—Chronic anterior gonorrhea, p. 491—Chronic posterior gonococcal infection, p. 496—Chronic anteroposterior gonorrhea, p. 500—Acute exacerbations of chronic gonorrhea, p. 500—Complications of gonorrheal urethritis and their treatment, p. 500—Determination of a cure, p. 512.

Gonococcal infection in the female, p. 513.

Gonorrheal vulvovaginitis in children, p. 517.

History of Gonorrhea.—Gonorrhea, a Latin word of Greek origin, is first found mentioned in the writings of Aretaios of Cappadocia, a Greek physician who lived in the first or second century. There are several references in the earlier literature which justify the belief that the disease was prevalent long before this period. It probably existed among the early Egyptians because in the Papyrus Ebers, the oldest medical Egyptian record, are found prescriptions to be used as injections for venereal affections. There is also a very accurate description of gonorrhea in a Japanese manuscript of 900 B.C. That the Jews did not escape is proven by verses in the fifteenth chapter of Leviticus.

By the end of the sixth century, some conception of the inflammatory nature of urethral disease had evidently been developed, because mention is made of pyuria, hematuria and dysuria. Paul of Ægina speaks of urethral suppuration and bleeding without admixture of urine.

It was not until 1000 A.D. that any attempt to explain the etiology of the disease was made. Maimon, a Jewish physician at Cairo (1139-1204), includes lasciviousness and licentiousness among the various causes. Guillaume de Salicet, in the thirteenth century, attributed the disease to impurities retained under the prepuce after connection with an unclean woman. He was the first to suggest prophylactic washing.

In the fifteenth century we find the history of gonorrhea merging with that of syphilis. In 1530 Paracelsus taught that gonorrhea was an initial symptom of syphilis. This misconception held sway until overthrown by the excellent work of Ricord, begun in 1831 and continued until 1860.

The personal experiment of John Hunter, in 1767, still further strengthened this erroneous belief. He unfortunately contracted both syphilis and gonorrhea from an inoculation of impure gonorrheal pus. His prominence in the medical world caused his teachings to be widely accepted and it was not until the middle of the eighteenth century that Ricord succeeded in convincing the medical profession of the duality of gonorrhea and syphilis.

Prevalence of Gonorrhea.—In civil life, sexual promiscuity and prostitution make the disease endemic. Because of the nature of the disease, it is impossible to obtain accurate statistics. It is highly probable that every male who indulges in promiscuous intercourse sooner or later acquires a gonorrhea. According to Morrow, 60 per cent. of the adult male population of the United States have gonorrhea. Forchheimer places the figure at 51 per cent. Among women gonorrhea is less common than among men. Statistics show the proportion of men to women as 16 to 1.

In 1901, there were reported 162,372 patients suffering from venereal disease in New York City; of these 90 per cent. had gonorrhea. During the year 1907, more than 12 per cent. of the men in the U. S. Army had gonorrhea. In the Philippines the percentage was higher, 18.71 per cent. The duration of the disease varied from twenty-three to fifty days.

Duration of Gonorrhea.—Experience has shown that the duration of the disease varies within wide limits, depending upon its extent, complications, and the habits and general condition of the patient. It has been stated that in acute anterior urethritis the average recovery takes place in five to six weeks. Yet we constantly see cases of acute anterior urethritis complicated by a persistent folliculitis or periurethral abscess which may last from eighteen months to two years. As Ricord states, "We know when gonorrhea begins, but God alone knows when it will end." When the gonococcus invades the posterior urethra and prostate the infection may persist for even three years or more. In general, it may be stated that the gonococci usually disappear from the urethra in six months, and rarely persist for more than two years. It is exceptional for gonococci to be present after two or three years, although cases have been reported in which they were demonstrated after longer periods.

In women, it is much more difficult to form any opinion. Many competent observers are unwilling to set any limit to its infectiousness. Many women, like men, may recover in a few months. In others, the duration is much more indefinite and the disease much more rebellious to treatment. Cases of vulvovaginitis in children have been known to persist for years.

Etiology.—In the adult the disease is in practically all cases acquired by coitus. The gonococcus is implanted from an infected cervix or urethra into the urethra of the male, reaching, in all probability, the fossa navicularis to which for a time its location is limited. The epithelium of the fossa navicularis is of the squamous type and resistant to the gonococcus. The organism probably lives in the secretions of the canal and at this stage is therefore easily destroyed or removed by suitable prophylactic treatment.

Extravenereal infection in adults is extremely rare. Cases have, however, been reported in which infection was transmitted by infected towels, lavatory seats and urethral instruments.

The gonococcus may be inoculated in the eye, urethra and the female genital passages. The rectal mucosa is more resistant. All squamous epithelium offers marked resistance. The mouth and nose are practically immune except in young children. The preputial cavity, the vagina of the female, and the urinary bladder are rarely and only mildly involved in gonorrhea.

That children and infants are very susceptible to gonorrhea is evidenced by the frequency of vulvovaginitis and gonorrheal conjunctivitis. Nasal and buccal gonorrhea occur almost exclusively in children.

Bacteriology of Gonorrhea.—Neisser, in 1879, made the first successful attempt to find the causative organism of gonorrhea. He was the first to describe the microscopic appearance of the gonococcus as seen in urethral and conjunctival pus. Other observers confirmed his findings, but all attempts to grow the organism in artificial media failed until Bumm, in 1885, successfully used solidified serum derived from the human placenta. The separation of the gonococcus in pure culture enabled experimental inoculation to be undertaken in the human subject, and the successful issue of these operations demonstrated the direct causal relationship of the gonococcus to the disease.

MICROSCOPICAL APPEARANCE OF GONOCOCCUS.—The gonococcus is a diplococcus. In shape it is planoconvex or bean-shaped and the pairs lie with their concave or plane surfaces opposing. They have no capsule, form no spores and are non-mobile.

They vary considerably in size. In purulent secretions they are found both within and outside of the pus and epithelial cells. The most characteristic groups are met with inside the cells. There is no definite clinical relationship between the extracellular or intracellular position of the gonococci and the severity or stage of the inflammation, in a given case. In every specimen, gonococci are found both within and outside of the cells and in no definite proportion.

STAINING OF THE GONOCOCCUS.—The gonococcus readily stains with any of the basic anilin dyes, e.g., methylene blue, fuchsin, gentian violet, etc. It is easily decolorized with alcohol, acids, xylol and other reagents. Thus in staining by the Gram process the gonococci lose their violet color and take up a counterstain. They are, therefore, *Gram negative.*

Many special methods of staining these cocci are described, but the Gram method is by far the most important as it differentiates the gonococcus from all Gram-positive organisms. When the Gram stain is applied, a thorough washing with alcohol leaves the gonococci colorless, while pseudo-gonococci stand out in bold relief, stained darkly by the combined color of gentian violet and the Gram solution. In order to demonstrate more clearly the effect of the Gram stain, a contrasting counterstain (fuchsin, etc.) is employed in order that the gonococci may be visible by direct comparison with other organisms.

In following up the effect of treatment it is not necessary to use the Gram method of staining. A 2 per cent. aqueous solution of methylene blue makes a very efficient and rapid stain.

Preparation of the Specimen.—To prepare the smear in a suspected case of gonococcal infection in the male, cleanse the external parts. Transfer some of the discharge in the meatus with a platinum loop to a glass slide. If there is extreme tenderness of the urethra, a drop of secretion may be expressed from the canal and transferred to the slide by direct contact.

In the female the material should be taken from the urethra and cervix. In chronic and doubtful cases, attempts should be made to obtain the secretions from Skene's and Bartholin's glands. After cleansing the parts with sterile water, the urethral discharge is obtained as in the male. Frequently if no secretion is visible a drop may be expressed by inserting a finger in the vagina and firmly stroking the urethra from above, downward and forward. The cervix is then exposed with a speculum, and the external os wiped dry with cotton. A platinum loop is inserted into the cervical canal and the secretion placed on a glass slide.

The pus is spread on the slide in a thin film. Each slide is then dried by evaporation at a gentle heat and fixed by rapidly passing it three or four times through a spirit lamp or Bunsen burner flame.

Methods of Staining.—(1) *Methylene Blue:* The specimen is covered with a saturated solution of methylene blue for ten seconds, washed in running water, dried and examined with an oil immersion lens.

(2) *Gram's Method:* The solutions employed are:

A. Anilin-water gentian-violet. This consists of

Anilin oil	3 c.c.
Absolute alcohol	7 c.c.
Distilled water	90 c.c.

Shake for two minutes. Filter until clear. Add two grams of Grübler's powdered gentian-violet. Set aside for twenty-four hours. Pipette supernatant fluid as required. This solution keeps well for 6 to 8 weeks. It takes time to prepare it, however, and it is quite unstable. The more stable carbolic-water solution of gentian-violet is recommended, consisting of:

	Saturated alcoholic solution of gentian-violet	1 part
	Five per cent. solution of carbolic acid	10 parts
B.	Gram solution.	
	Iodin	1 part
	Potassium iodid	2 parts
	Distilled water	300 parts
C.	Absolute alcohol.	
D.	Contrast stain.	
	Carbolic acid	2 parts
	Saturated aqueous solution of Bismarck brown	98 parts
	or	
	Carbolfuchsin (Ziehl-Neelsen)	1 part
	Water	20 parts

Technic of Staining.—(1) Stain with anilin-water gentian-violet or carbol-gentian-violet for three minutes. Shake off excess of stain.

(2) Cover with Gram's iodin solution for two minutes.

(3) Decolorize with absolute alcohol for thirty seconds.

(4) Allow to dry.

(5) Counterstain with Bismarck brown or carbolfuchsin solution for three to five minutes.

Value and Limitations of Staining Methods.—For ordinary clinical work, the Gram method of staining is employed to distinguish the gonococcus from the staphylococci and other Gram-positive cocci. There are three sources of error, viz.:

(1) There are other Gram-negative cocci from which the gonococcus can be distinguished only by culture, such as the *Micrococcus catarrhalis, Diplococccus intracellularis* and certain chromogenic cocci. None of these organisms except the *Micrococcus catarrhalis* have been identified in the genito-urinary tract and none of them except the *Micrococcus catarrhalis* is believed to cause urethritis. The urethritis caused by the *Micrococcus catarrhalis* is rare and could not clinically be mistaken for acute gonorrhea.

(2) In a small percentage of cases in the normal urethra and also in the normal vagina, Gram-negative cocci are found. They can usually be differentiated from the gonococcus by their form, size and extracellular position.

(3) The fact that staphylococci may be Gram-negative as well as Gram-positive is a frequent cause of error.

These confusing factors apply almost exclusively to chronic urethritis. For all practical purposes, in cases of acute urethritis the presence of Gram-negative coffee-bean-shaped, intracellular diplococci is diagnostic of gonorrheal infection, when supplemented by the usual clinical evidence.

The methylene blue stain has no differential value. It is useful only because it is a quick method for studying the effects of treatment in a given case in which the diagnosis has previously been made by the Gram method. Neither the Gram nor methylene blue stain should be relied upon to verify a cure of gonorrhea. *In order to establish a diagnosis beyond a doubt the isolation and identification of the specific organism is the only certain method.*

In acute cases, the gonococcus can usually be cultivated from the discharge without much difficulty, providing suitable culture media are employed. In chronic cases more difficulty is met with, and even when the greatest care is used in securing the material for examination and preparing the culture, repeated examinations are necessary before a definite opinion can be given.

In chronic cases or those in which a cure is to be determined, the method of obtaining material is as follows: The patient is instructed to report with a full bladder. After cleansing the parts with green soap and a 1-60 carbolic acid solution, the patient voids several ounces of urine into a sterile flask. The prostate and vesicles are then thoroughly massaged, after which the patient is instructed to void the remainder of the urine in a second sterile flask. The specimens, while warm, are immediately sent to the laboratory. Chilling of the samples reduces the chances of success. On the other hand prolonged exposure to body temperature permits the growth of other contaminating organisms which renders the isolation of the gonococcus more difficult.

For the initial culture of the gonococcus, either Wertheim's ascitic agar or Heiman's culture media is employed. For a detailed consideration of the preparation of the various culture media, and the cultivation and isolation of the gonococcus, the reader is referred to special works on the subject.

GONOCOCCAL IMMUNITY REACTIONS.—In addition to their scientific interest, the immunity reactions which can be excited by the gonococcus have an important practical bearing on certain methods of diagnosis. Their as yet incomplete development and interpretation have been due to the failure of all attempts to produce gonococcal infections in animals. No toxins seem to be elaborated by the gonococcus, but Wassermann and others have shown, by means of the complement-deviation test, that bodies similar to amboceptors were present in the blood of patients suffering from gonococcal infection. Since then much work has been done on the complement-deviation test, on opsonic action and agglutinations. The results, though far from complete, serve to substantiate the view that a specific immunity is elaborated in the human organism against the gonococcus.

Complement-Deviation Test.—The credit for having made the test of clinical value belongs to Schwartz and McNeil. The reactions depend upon the fact that, in the presence of the complement, gonococcal endotoxins (antigen) combine with gonococcal antibodies (patient's serum), and that, in doing so, the complement (guinea-pig serum) becomes "fixed" or "deviated." The fixation of the complement which occurs if gonococcal antibodies are contained in the patient's serum prevents lysis of the red cells and a "positive" reaction is then said to have been obtained.

According to Schwartz and McNeil, in cases of anterior gonorrheal urethritis in the male, and acute vulvovaginitis in the female, a positive reaction is rarely obtained. When, however, the infection invades the posterior urethra in the male, and the cervix, glands of Bartholin and the pelvic organs in the female, the patient will react positively. The test becomes positive sooner or later in posterior urethritis, prostatitis, seminal vesiculitis, epididymitis, cystitis, pyelonephritis, arthritis, etc. A positive reaction persists six to eight weeks after a cure is effected. If a strong positive reaction persists *after* this period, the case should be regarded as still harboring gonococci.

(1) *Effect of Vaccines on the Test.*—If gonococcus vaccines are given to a patient with a fading or weakly positive test, the vaccines will change the weakly positive to a strongly positive test. If the patient has not recently had a gonorrhea, vaccines will have no effect upon the test.

(2) *Clinical Value of the Test.*—The accuracy of the test will vary according to the skill and experience of the serologist. Technical errors interfering with the validity of the test are much less likely to occur than in a gonococcus culture. On the other hand, a positive culture is more certain evidence that the gonococcus persists in the urethra or vesicles, than is a complement-fixation test. Thus if a patient has a gonorrheal arthritis as shown by a positive complement-fixation test, bacteriological examination is necessary to prove that gonococci are present in the urethra. On the other hand, the test will often help to differentiate between rheumatic and gonorrheal arthritis.

As previously stated, the results obtained will vary with different observers; thus Keyes made a careful comparison between the relative merits of the "fixation" test and bacteriological examination. In 100 cases, the complement-fixation test was wrong in 1 out of 47, the bacteriological test in 1 out of over 100 examinations.

In the authors' work, the test has proven of most value in acute posterior urethritis, prostatitis, vesiculitis, arthritis and systemic gonorrhea. A positive test means that gonococci are present in the body, bearing in mind that the reaction may persist from 6 to 8 weeks after a cure. In chronic gonorrheal prostatitis and vesiculitis, the results have not been so satisfactory, the test at times being negative when careful bacteriological examinations later demonstrated gonococci in urinary shreds or in the discharge.

In uncomplicated anterior urethritis, the test is of no value, a clear urine and negative bacteriological findings being necessary to determine a cure. In two clinic patients suffering from a hyperacute anterior gonorrhea, one complicated by periurethral abscess and the other by balanoposthitis, a positive fixation was obtained.

In conclusion it may be said that a positive fixation test signifies the presence of gonococci in the body. A negative test is not so reliable. This fact must be borne in mind when the test is employed in the determination of a cure. Variations in the different strains of gonococci may probably explain some of the misleading negative reactions and the persistence of antibodies in the blood after all gonococci have been exterminated may account for erroneous positive results.

Gonococcus Vaccines.—Either stock or autogenous vaccines are employed in the treatment of gonorrhea. Autogenous vaccines have the advantage of being specific in a given case. They have the disadvantage, however, in that it takes several days to prepare them and are, therefore, not available when needed. The experiments of Teague and Torrey showed that the serum of an animal immunized to one strain of gonococcus did not cause fixation of complement when tested against an antigen obtained from another strain. They were able to differentiate eleven strains of gonococci. Most of the stock vaccines now sold are a mixture of different strains and are commonly employed when beginning the treatment.

(1) *Dosage.*—This varies with different urologists from 10,000,000 to 50,000,000. We usually begin with 50,000,000 and increase 25,000,000 at each dose until a maximum of 200,000,000 is reached. The injections are given intramuscularly, preferably in the gluteal region, and are not repeated oftener than every other day.

Local pain and inflammatory reaction following injection are usually mild. General febrile or toxic reactions sometimes occur, if the dosage is high or pushed too rapidly. They rarely last more than twelve hours.

(2) *Results.*—In acute or chronic urethritis and vulvovaginitis we have never seen any benefit derived from the use of vaccines. In acute prostatitis, epididymitis, vesiculitis or periurethral lesions, the employment of vaccines frequently seems to lessen the severity and duration of the disease. When a patient with gonorrhea develops fever or symptoms suggestive of these complications the prompt use of vaccines may perhaps abort them. In systemic gonorrhea, many authorities rely upon frequent injections ranging from 50,000,000 to 600,000,000. In gonorrheal sepsis the results are sometimes very definite, in others they are entirely negative.

Antigonococcus Serum.—Rogers and Torrey employ a polyvalent serum obtained from the ram. It is also prepared from rabbits, sheep and horses. The serum of the former is preferred because it seems less toxic. The animals are immunized by injections of increasing doses of gonococcus emulsion. The serum is tested for its gonococcus antibody content by means of the complement-fixation test.

(1) *Dosage.*—This varies from 2 c.c. to 25 c.c. at 24 to 48-hour intervals. When ram serum is used, a local reaction may occur, characterized by a varying amount of swelling, redness and tenderness.

(2) *Results.*—In localized gonorrhea and its complications, the results are variable and perhaps inferior to those of the vaccines. In systemic gonorrhea and in joint cases, Rogers reports good results in 85 per cent. of early cases. Herbert reports satisfactory results in all chronic joint cases. Swinbourne states that when the serum was employed at the onset of 27 cases of acute epididymitis, the pain was relieved in 24 hours. Watson has employed it in the vaginitis of children without result.

BACTERIOLOGY OF CHRONIC GONOCOCCAL INFECTION.—*Chronic Urethritis.*—The existence of a mixed infection, in chronic urethritis, is due, in most cases, to the various types of bacteria which are found under normal conditions in the urethra. In a general way, it may be stated that chronic urethritis may be due to:

(1) The persistence of the gonococcus.

(2) Presence of the gonococcus in conjunction with other bacteria.

(3) Other bacteria without the gonococcus.

As previously stated, the gonococcus in the male is rarely found after three years. Notthaft, who states that the gonococcus always disappears from the prostate within three years, is supported in his belief by Finger, Wassidlo, Goldberger, Neisser, Frank and others. The bacteria in normal urethræ have been studied by various observers. Pfeiffer examined 24 normal subjects and found diphtheroid bacilli in 21, streptobacilli in 10, *Staphylococcus pyogenes aureus* in 5, *Micrococcus candicans* in 4, *Sarcina alba* in 14. Petit and Wassermann found 5 varieties of cocci, 6 kinds of bacilli. Franz, in 56 urethras, found the sarcina once, *Bacillus coli communis* once, *Staphylococcus pyogenes* 6 times, streptococci twice, and 7 other varieties of cocci and four of diplococci. These bacteria were found, in practically all cases, near the meatus. Very few, or none, were found in the deeper portions of the anterior urethra.

Chronic Anterior Urethritis.—In 154 cases, examined by Tano, Cohn, Owens and van Hoffmann, 10 showed gonococci alone, 10 gonococci mixed with other bacteria, 114 other bacteria without gonococci; 20 were sterile.

Chronic Prostatitis.—Young, Geraghty and Stevens examined 17 cases. They obtained a growth on agar in only eight. The staphylococcus was found in 3 and *Streptococcus pyogenes* in 2. Notthaft examined 120 cases. He found the gonococcus 47 times, other micrococci, 119, bacilli, 15, other bacteria, 14 times. Cohn in 12 cases found *Staphylococcus albus* 11 times, streptococcus 3 times, bacillus coli once, other bacteria 3 times, no gonococci. The gonococcus was not found after the third year. He found the gonococcus in only five cases within 18 months of the time of infection. In cases of less than 18 months, the gonococcus was found in 60 per cent., either alone, or with other bacteria. In cases ranging from 18 months to 2 years, the gonococcus was found in 18 per cent. Cases of from 2 to 3 years' standing showed gonococci in 6 per cent.

Chronic Vesiculitis.—Gonococci are rarely found. Cultures are often sterile. The usual bacteria present are staphylococcus, streptococcus, *Bacillus coli communis* and *Bacillus lactis aërogenes.*

INCUBATION PERIOD.—This varies from two days to two weeks. The average incubation period is from 5 to 7 days. In inoculation experiments the incubation period is from 2 to 5 days. The shortest incubation periods are probably due to a combination of simple urethritis or sexual strain with gonococcal infection. Exacerbations develop, as a rule, more quickly than new infections.

According to Keyes, the average incubation period of 34 primary attacks was 6 days. Of these the primary attack in 20 per cent. appeared before the fifth day, in 61 per cent. on the fifth, sixth and seventh days. In 76 secondary attacks, the average incubation period was 4.88 days, of which 55 per cent. appeared before the fifth day, and 31 per cent. from the fifth to the seventh day.

Pathology of Gonococcal Infection.—Wherever the gonococcus is found, tissue changes characteristic of bacterial invasion are soon apparent. The organism at first grows on the surface of the epithelium, forming surface colonies. The production of toxins by the gonococci soon causes hyperemia and serous exudation. The cylindrical epithelial cells become swollen and loosened and cast off in great numbers. The smaller blood-vessels are seen crowded with leukocytes, and diapedesis and leukocytosis are soon in active process, causing the characteristic purulent discharge. The concentration of the wandering cells is greatest immediately below the epithelial layers.

Squamous epithelium is more resistant to the gonococcus and, although colonies may flourish on the surface, they do not penetrate between the interstices of the cells. In the case of cylindrical epithelium, gonococci readily reach the corium and, frequently, also the submucous tissue. Wherever the gonococci penetrate, there is intense infiltration in proportion to the number of organisms. As the gonococci pass along the lymph-channels, they set up more or less lymphangitis. As the purulent stage subsides, the denuded areas of epithelium are regenerated and layers of flattened cells are formed.

ACUTE ANTERIOR URETHRITIS.—We are indebted to the writings of Finger, Gohn and Schlagenhaufer for the pathological findings in acute anterior urethritis. The urethræ of condemned criminals were inoculated, and immediate postmortem examinations were made to investigate the various stages of invasion of the tissues by the specific microbe. Thirty-eight hours after inoculation, the gonococci had only just begun to penetrate between the epithelial cells. At the end of three days, the surface of the epithelium was covered with pus, the epithelium being infiltrated with bacteria on one side, and by leukocytes on the other. The inflammatory changes showed striking characteristics:

(1) The squamous epithelium of the fossa navicularis resisted the invasion of the gonococci almost absolutely.

(2) The cylindrical epithelium of the penile urethra showed extensive invasion, most marked about the crypts and glands, which were packed with pus and gonococci.

(3) The subepithelial connective tissue contained few gonococci, except in the neighborhood of glands and crypts. Definite inflammatory changes, however, were present.

The glands and crypts are implicated in the general inflammatory process and form important centers of inflammation. Their orifices frequently become closed by the swelling of the mucous membrane. Since the gonococci often extend to, and sometimes into, the corpus spongiosum, the suppuration and periglandular infiltration arising is often very intensive and extensive at the height of an acute gonorrhea.

CHRONIC ANTERIOR URETHRITIS.—There is a distinct tendency in a considerable proportion of cases for the processes which are productive of cure to stop short of completeness, causing a so-called chronic inflammation, which allows the gonococcus to maintain its existence in certain areas, although its activities are restrained. The following pathological changes are noted:

(1) The periglandular inflammatory exudate is gradually converted into cicatricial tissue. The extent and density of the connective tissue formation will depend upon the intensity and distribution of the acute inflammation.

(2) Changes in the glands and crypts are seen. The inflammation within them may persist, resulting in the "glandular urethritis of Oberlander." The opening of the gland may become occluded, causing the formation of a purulent or colloidal cyst (dry urethritis of Oberlander). The inflammation may cease, either by a return to the normal, or by cicatricial obliteration of the gland. These changes may all be seen in the urethra at the same time.

(3) Changes in the mucous membrane are those of chronic inflammation. They may be general, or localized over one or more small areas. The type of inflammation will depend upon the degree of infiltration and sclerosis. If the sclerosis is slight and infiltration predominates, the urethroscope shows the surface to be swollen, red and eroded in spots, while here and there appear the inflamed orifices of suppurating glands. This stage has been termed the "soft infiltration of Oberlander." When there is marked sclerosis, the overlying mucous membrane is lighter in color than the adjacent healthy mucosa and appears salmon-colored or dirty grayish yellow. Elsewhere there may be ulcerations, erosions, papillary outgrowths, with here and there a patch of squamous epithelium. This is the "hard infiltration of Oberlander." When the sclerosis is still more marked and extensive, urethral stricture results, diminishing the caliber of the urethra. The soft infiltration may heal spontaneously by absorption; the hard infiltration requires dilatation and leaves a permanent scar.

MEMBRANEOUS URETHRA.—Inflammation of this portion of the urethra is clinically mild. Submucous infiltrations are usually slight and stricture is rare. The glands are relatively few and simple and chronic glandular catarrh is comparatively mild.

PROSTATIC URETHRA.—In this part of the canal the glands are large and complex. Gonococcal infection often causes abscesses in the glands which break through into the canal. The verumontanum and sinus pocularis may also be the seat of abscess formation.

THE PROSTATE.—When the prostatic urethra is involved there is practically always some involvement of the prostate. Prostatitis is perhaps the most frequent and important complication of genital gonorrhea in the male. In the milder forms, the inflammation extends into the ducts and either spares or does not markedly involve the acini (catarrhal prostatitis), with very little or no infiltration of the stroma. When the acini are involved they become distended with pus, with infiltration of the surrounding stroma. When the inflammation becomes chronic, the involved acini may continue to suppurate or become cystic, necrotic or atrophic, with induration of the interstitial tissue (follicular prostatitis). When the inflammation is more intense, there is a more marked involvement of the stroma. Abscesses may form in small multiple foci, few or many of which may resolve or coalesce to form a large abscess, which usually ruptures into the urethra or, more rarely, into the ischiorectal fossa or rectum.

CHRONIC PROSTATITIS.—According to Young, Geraghty and Stevens, the microscopic changes are as follows:

"Periacinous infiltration is the essential lesion of chronic prostatitis. This frequently exists alone or may be combined with interstitial and endoglandular processes. The changes in the acini are manifold. In some instances the cul de sacs are dilated; this dilatation may be due to stricture or obstruction in the excretory ducts, but it is probably more often the result of an accumulation of inflammatory products in the glandular sacs, the muscular tone of whose walls has been injured by the inflammatory process. Acini, however, the caliber of whose lumina has been diminished, are almost as frequently seen as are dilated ones, and this is especially true where the prostatitis has been of long standing and an extensive periacinous sclerosis has formed. At times the acini are mere vestiges or may be entirely replaced by fibrous tissue in areas of considerable extent. The acini are often partially or entirely filled with proliferating and desquamated epithelium."

SEMINAL VESICULITIS.—In acute gonorrhea the vesicles undergo the same changes as are found in the prostate. Abscess of the vesicles is rare. In chronic inflammation the walls of the vesicles are infiltrated. In severe cases or in those of long standing, a perivesicular infiltration is often found. As the condition becomes more chronic, the round-cell infiltration becomes organized and contracts, causing occlusion of the lumen. The gland does not drain and frequently in long-standing cases the vesicle, instead of being a branched ramifying canal, is converted into an irregular cavity containing pus.

GONORRHEA IN THE MALE

When gonococci are implanted upon the urethral mucous membrane, they multiply and produce an inflammation which, under favorable conditions, may terminate in the anterior urethra without invading the posterior urethra. Usually, however, after the organisms have been multiplying for some time in the anterior urethra, they gradually extend backward and invade the posterior urethra. The inflammation may invade the prostatic ducts and infect the prostate, or it may involve the seminal vesicles by extension through the ejaculatory ducts, or by further extension downward through the vasa deferentia, invade the epididymes and testicles. Although the organisms may reach the bladder by the back flow of pus from the deep urethra, the latter is rarely involved. The same is true for the ureters and kidneys. Although it is quite possible for these organs to be involved by direct extension, the hematogenous route is in all probability the usual route. Once the posterior urethra and prostate are invaded the organisms may find their way into the blood stream and give rise to metastatic lesions.

In describing gonorrhea and its complications, we should, strictly speaking, consider anterior gonorrheal urethritis as the essential condition and class all other gonorrheal inflammations, including posterior urethritis, as complications; because under favorable conditions gonorrheal inflammation of the anterior urethra may terminate, as such, without involving the deep urethra. In the average gonorrhea, however, the deep urethra is usually involved. In as much as the symptomatology of anterior urethritis differs so much from that of posterior urethritis, it is clinically more convenient to consider them separately in the type description of the disease and to consider other gonorrheal inflammations as complications of one or the other. Accordingly, we shall describe in the course of this article:

(1) *Acute anterior gonorrheal urethritis:*
Complications: Abscess of urethral glands.
Periurethral abscess.
Inflammation of erectile tissue.
Balanoposthitis.
Adenitis.

(2) *Acute posterior urethritis:*
Complications: Prostatitis, Prostatic abscess.
Seminal vesiculitis.
Epididymitis.
Pyelitis, Pyelonephritis.

(3) *The metastatic lesions include:*
Bacterial lesions: Arthritis.
Endocarditis.
Iritis.
Bursitis, Tenosynovitis.
Periostitis, Osteitis.
Myositis.

(4) *Rare forms:*
Anorectal gonorrhea.
Buccal gonorrhea.
Nasal gonorrhea.

SYMPTOMATOLOGY OF GONORRHEA IN THE MALE

Acute Anterior Gonorrheal Urethritis.—In the beginning a slight tickling itchy irritation is felt at the meatus. The lips may be adherent, or a small amount of bluish sticky discharge may be seen between them.

A slight burning or stinging on urination is next experienced. This may last a day or two, when the meatus begins to swell and redden. The discharge increases in amount and becomes frankly purulent, varying in color from a creamy yellow to a greenish color. The *symptoms* are:

(1) Swelling of the meatus.
(2) Purulent discharge.
(3) Painful urination.
(4) Chordee.

(1) *The Meatus.*—At first the meatus is glued together, later the lips are red, swollen and everted and in very severe cases eroded. To the experienced observer, this appearance of the urethral orifice is almost pathognomonic of gonorrhea. Usually by the end of the second week, the swelling and redness subside and disappear, long before the inflammation in the deeper parts of the canal has terminated. In secondary attacks, and in acute exacerbations of chronic urethritis, the involvement of the meatus is less constant and less marked.

(2) *The Discharge.*—This at first is serous and opalescent, later as pus is formed it assumes a milky color. When the inflammation is at its height, it consists of greenish yellow pus, occasionally streaked with blood. In the subsiding stage, the pus ceases to be thick and gradually becomes paler in color, finally diminishing in amount and becoming more watery in quality.

(3) *Painful Urination.*—The passage of urine is painful and slow and somewhat obstructed, because the mucous membrane is swollen, eroded and sensitive. The pain on urinating reaches its height usually by the end of the first week and begins to subside after the second week.

(4) *Chordee.*—Chordee or painful erections are of frequent occurrence. The irritation produced by the inflamed mucous membrane causes erections, especially at night. The infiltration of the urethral mucosa and spongy tissues of the corpus spongiosum renders them relatively inelastic, hence the stretching of the tissues during erections becomes exceedingly painful. The corpora cavernosa retain their elasticity so that when the penis is erected it is curved downward.

Examination of the Urine.—The urine voided into a glass appears turbid. This turbidity is due to pus, mucus and desquamated epithelium. As the case goes on to recovery the urine gradually becomes clearer and finally transparent, containing filaments or so-called "clap shreds." These latter, on microscopic examination, are seen to be made up of pus cells, desquamated epithelium and mucus, with or without gonococci. Their presence indicates that isolated eroded portions of mucous membrane are not covered with epithelium and are still secreting pus.

The "two-glass urine test" should be made at each visit to determine:

A. The amount of pus excreted.
B. Whether the posterior urethra is invaded.

The diagnostic value of the so-called "glass tests" will be discussed later.

***Examination of the Smear.*—Although in rare instances, about 1-5000, the *Micrococcus catarrhalis* may be the exciting cause, the finding of a Gram-negative intracellular diplococcus, in conjunction with the characteristic clinical signs, clinches the diagnosis for all practical purposes. Only in medico-legal cases is a culture necessary.**

At the onset of the disease, the smear shows quantities of desquamated epithelium, pus cells and mucus. Clumps of intracellular and extracellular gonococci are seen.

At the height of the inflammation the pus cells predominate and many gonococci are present.

During the stage of decline the pus cells are diminished in number and fewer of them contain gonococci. Epithelium is present in larger amounts. As the case goes on to a cure, the gonococci disappear and the discharge or urinary sediment contains only desquamated epithelium, mucus and an occasional pus cell with no gonococci. It is rare for the gonococci and pus to disappear within six weeks. They usually persist from 8 to 12 weeks.

The methylene blue stain should be used as a routine method during the course of the disease to determine the efficacy of the treatment.

Acute Posterior Gonorrheal Urethritis.—The frequency with which posterior urethritis develops in acute gonorrhea varies with different observers from 60 to 90 per cent. This variance is probably due to the type of patients studied. Among the laboring classes, such as frequent the clinics, the percentage of posterior involvement is undoubtedly higher. Prostatitis is estimated to complicate from 70 to 80 per cent. of the cases of acute posterior urethritis.

Posterior urethritis usually develops between the seventh and fourteenth days.

The *symptoms* of posterior invasion are all referable to acute inflammation of the vesical neck, as is also the appearance of pus in the second flow of urine.

(1) *Frequency and Urgency of Urination.*—Because of the acutely inflamed hypersensitive condition of the mucous membrane of the prostatic urethra and trigon, the accumulation of relatively small amounts of urine in the bladder causes an intense desire to urinate. This may be so great, in severe cases, that the patient dribbles away a few drops of urine every 15 minutes. In anterior urethritis the patient urinates as infrequently as possible, in order to escape the pain of urination. In posterior urethritis the call to urinate is so imperative that *he must urinate.* The frequency and urgency is present during the night, although less marked than in the daytime. Yet it may be intense enough to cause a sleepless night, unless measures are taken to relieve it. In the milder cases there may be practically no frequency or urgency.

(2) *Painful Urination.*—The pain on urination in posterior urethritis is very characteristic. It may be referred to the perineum, rectum, epigastrium or to the anterior urethra. It appears just before the act in the form of urgency. During urination it may be felt either in the

perineum, rectum or anterior urethra, but it is toward the end of the act that it is felt most acutely. The contractions of the bladder and urethra in attempting to expel the last drops of urine, cause a series of spasmodic pains which may persist for several minutes, even after the bladder has emptied itself.

(3) *Terminal Hematuria.*—This is caused by the terminal spasm. In severe cases the last jet of urine may be almost pure blood. In mild cases it is not present. The bleeding may be constant or intermittent. In either case the amount of blood lost is not great.

(4) *The "Two-Glass Test."*—In acute posterior urethritis the pus which forms in the deep urethra flows back and becomes mixed with the bladder urine. The second urine voided is therefore always turbid.

Chronic Gonorrhea.—By common consent a gonorrhea of less than two months' duration is called acute. When it persists for more than three months it is considered chronic. This distinction is purely an arbitrary one and serves to emphasize the fact that while in some cases gonorrhea may be cured in two months, in others there is unfortunately a distinct tendency for the processes which bring about a cure to stop short of completeness and for the gonococcus to maintain its existence in certain areas, either alone or in conjunction with other organisms.

In chronic gonorrhea, gonococci are most frequently found in gland ducts, either in the anterior urethra (gonorrheal folliculitis), or in the posterior urethra (chronic gonorrheal prostatitis). They may also survive for some time in the mucosa. In either situation it is difficult to reach them with any local antiseptic. In the presence of continuous irritation, the surrounding infiltration, usually of periglandular localization, instead of becoming absorbed, undergoes a series of changes, resulting eventually in the formation of cicatricial tissue. Clinically the different stages are recognized as "soft" and "hard" infiltrations. The final end result in unfavorable cases is stricture.

In order to distinguish the symptoms of anterior urethritis from those of posterior, both conditions must be studied separately. Clinically, however, the two usually exist together, either one or the other predominating.

CHRONIC ANTERIOR URETHRITIS.—Chronic anterior urethritis is characterized by:

(1) Urethral discharge.
(2) Tendency for acute exacerbations.
(3) Pain, itching or burning in the urethra.
(4) Urinary signs.

(1) A *urethral discharge* is the one subjective symptom of chronic anterior gonococcal urethritis. It varies in quantity, and is purulent, mucopurulent or mucoid in appearance. At times the discharge is profuse, at others it is very scant or may not show at the meatus, simply appearing in the urine in the form of urinary shreds. In others, owing to the more frequent flushings of the urethra with urine during the day, no discharge is seen, but over night sufficient discharge collects and appears as a "morning drop."

(4) *Urinary Signs.*—These constitute an important element in the diagnosis and will be discussed later.

STRICTURE.—This very important complication will be considered separately.

CHRONIC POSTERIOR URETHRITIS AND CHRONIC PROSTATITIS.—Chronic posterior urethritis is always complicated by some involvement of the prostate. In fact, it is clinically impossible to differentiate one from the other. Hence it is preferable to consider chronic posterior urethritis in conjunction with chronic prostatitis.

The *symptoms* of chronic inflammation of the posterior urethra and prostate as classified by Young are as follows:

(1) The urinary symptoms are urethral discharge, disturbances of urination and mechanical obstruction to urination.

(2) The referred symptoms are reflex pains and abnormal sensations.

(3) The sexual symptoms are sexual disturbances, spermatorrhea and prostatorrhea.

(1) *Urinary Symptoms.*—If no anterior inflammation is present, then no urethral discharge is seen. Since, however, posterior inflammations complicate about 80 per cent. of chronic anterior urethritis, the patient's complaint of a persistent discharge should warn the physician of the possibility of an accompanying posterior inflammation, because such urethral discharges can only be cured by the combined treatment of the anterior and posterior inflammations.

Urination may be normal, or there may be frequency and urgency of variable intensity. At times there may be pain before or during the act. Although urinary obstruction is infrequent, the stream may be weak, slow to start, with more or less dribbling. This may be due to turgescences of the mucosa of the deep urethra, swelling of the verumontanum, the formation of a median bar or to cicatricial contraction of the vesical neck. The symptoms in the more marked cases are those of prostatism in a young person, without enlargement of the prostate as felt by rectum.

(2) *Reflex Pains.*—The characteristic pains of chronic posterior urethritis and prostatitis are in the back, above the pubis, in the perineum, in the groin, testis, or along the urethra.

Pain in the back is usually felt in the sacrum and lower lumbar vertebra, rarely over the kidneys. It may be a constant dull ache or may be most pronounced in the morning, disappearing during the day.

Erotic excitement, repressed sexual desire or excesses tend to aggravate it. In one of our patients, a physician, the pain was most marked at night, and was intense enough to cause insomnia. This was promptly relieved when local treatment of the prostate was begun.

Perineal Pains.—These may be mild or very annoying. The patient is usually nervous and irritable. He cannot sit in one position for any length of time, but shifts about continuously to relieve the symptom, which is evidently due to continued pressure against the perineum. He frequently complains of a dull ache, burning or sense of fullness in this region.

Urethral Pains.—These may be present in the perineum or they may be referred to a point just behind the glans or to the penoscrotal junction. In some cases a numbness of the glans is complained of.

(3) *Sexual Disturbances.*—These are nearly always present. The sexual appetite is disturbed. There may be a constant desire for intercourse which is not satisfied by indulgence, or there may be no inclination for coitus which, if indulged in, is followed by a condition of general nervous depression. Premature ejaculation occurs on account of the hypersensitive, irritable condition of the posterior urethra and, for the same reason, nocturnal emissions may occur. As the condition advances, erections cease entirely and impotence is the final result.

Prostatorrhea and Spermatorrhea.—As a result of chronic inflammation of the prostate, functional disturbances, such as urethrorrhea, prostatorrhea and spermatorrhea are frequently encountered. Unless the case is of long standing proper local treatment and a carefully regulated sexual hygiene corrects them in time.

CHRONIC GONORRHEAL VESICULITIS.—Chronic vesiculitis is always associated with chronic prostatitis and posterior urethritis. In addition to the sexual symptoms noted above the following may be complained of when the vesicles are involved.

Rectal Pains or Vesicular Colic.—These are felt high up in the rectum, and are usually spasmodic and griping in character. They may be brought on by erection, straining at stool, ejaculation, or may occur spontaneously. Sometimes the pain is felt so high up that it simulates renal colic.

Painful Testicle.—Neuralgia or irritability of the testicle may be due to a reflex pain from a corresponding diseased vesicle. It consists of a sensitiveness of the whole gland or some portion of it. Mere contact of the clothing may be exquisitely painful. When vesiculitis is the cause, treatment will relieve the condition.

Gonorrheal Rheumatism.—Fuller first suggested that chronic seminal vesiculitis was the cause of gonorrheal rheumatism. This will be considered under rheumatism.

DIAGNOSIS OF GONORRHEAL INFECTION

In the diagnosis of gonorrhea involving the lower urinary tract and the genital organs in the male, two essential features are necessary:

(1) Discovery of the gonococcus; (2) diagnosis of the seat of the lesion: first, in acute urethritis, second, in chronic urethritis.

It is advisable to have some routine method when patients present themselves for examination, otherwise important features may be overlooked.

The writers have found the following method most practical and suitable for both private and clinic practice:

History of the Case.—A careful history is taken; this includes:

- Past History
  - Number of previous attacks.
  - Duration of previous attacks.
  - Complications.
  - Condition after treatment.
- Present History
  - Duration.
  - Incubation.
  - Discharge.
  - Pain (character, location).
  - Character of urination (force, quantity, frequency, precipitancy, tenesmus, dribbling, hesitancy, etc.).

Examination of Male Patient Standing.—External Genitals.—The size, shape or malformations (hypospadias, epispadias, etc.) are noted. The condition of the glans and prepuce and the presence or absence of ulcerations, verrucæ, abscesses, lymphadenitis, etc., are next determined.

The *meatus* is next inspected. Its size and shape are noted. If there is a urethral discharge, a smear is taken for microscopic examination. If the discharge is scanty, it is sometimes possible to obtain a sufficient amount by pressing upon the urethra from behind forward. If there is an induration at the meatus with the lips pressed together it may indicate the initial lesion of syphilis, whereas if ulceration is present, chancroid may be the cause. Ulceration with induration associated with a thin bloody discharge may mean either syphilis with mixed infection or a cancerous lesion originating in the urethra (in the aged). If the lips of the meatus are red, swollen and exude a creamy discharge, then gonorrhea is the most probable cause. To confirm this and to afford the patient the advantages of early local treatment, the microscope is necessary for immediate diagnosis.

The Urine.—The patient passes a portion of his urine into a glass cylinder. The color, transparency and presence of shreds and mucus are noted.

He is then asked to void a second portion of urine, retaining some in his bladder. The second urine is inspected the same way.

Prostate and Vesicles.—This is a very important part of the examination and should never be omitted, otherwise important information of the nature, extent and chronicity of the disease may be missed. The patient bends forward, resting his hands on a table. The examiner places a finger cot on his forefinger, lubricates it with vaselin and inserts it in the rectum. By placing the fingers of the left hand in the groin of the patient and making counterpressure, the vesicles can be more easily palpated. Some urologists advise first distending the bladder with boric acid solution. This is not necessary and is employed only in subjects with narrow pelvic outlet, in which the prostate and vesicles seem high up, out of reach of the finger.

The examiner notes the shape, size, consistency and tenderness of the parts. Gentleness is essential. Rough, jerky movements frighten and hurt the patient, making him strain and rendering the examination useless. An intensely hot, swollen, tender, enlarged, turgid gland with one or both lobes involved points to acute prostatitis. Nodules in the prostate show local areas of follicular inflammation, either gonorrheal, simple chronic or tuberculous.

A prostate which is soft and boggy indicates chronic atonic prostatitis. An enlargement of the gland with nodular swellings, indurations and depressions, without acute symptoms, points to tuberculosis. In elderly men an enlargement denotes hypertrophy or malignancy or both. When the prostate is small, irregular in outline with depressions and soft areas, it signifies that former abscesses have destroyed a part of the prostatic tissue.

Normal vesicles cannot be outlined when empty. In young vigorous adults who practice continence or indulge rarely in intercourse, varying degrees of distention are met with. This does not necessarily imply disease. In acute inflammations the vesicles are engorged, thickened and tender. Distended tender vesicles point to a sub-acute process or to congestion with retention of vesicular secretion.

In chronic inflammations, the vesicles may have thickened or atonic flabby walls. They may be nodular or irregular in outline due to scar formation or stricture. Small, stringy, hard and irregular vesicles are the result of chronic inflammation with partial destruction.

The Third Urine.—During the examination of the prostate and vesicles the organs are gently massaged with the finger, after which the patient is told to void his urine in a third cylinder. The three urines are then examined separately for bacteria, pus, mucus and epithelium. The first urine contains the washings of the urethra plus any elements from the bladder, ureters and kidneys. The second represents that from the bladder, ureters and kidneys alone, *assuming that sufficient urine was passed in the first portion to flush out the urethra.* The third urine contains, in addition to the second urine, the products massaged from the prostate and vesicles.

The careful microscopic examination and comparison of these urines often give valuable information to the surgeon regarding the nature and intensity of the pathological process. They should not, however, be solely relied upon to *localize* inflammatory processes in the anterior and posterior urethra or in the prostate and vesicles.

Many physicians have the erroneous impression that the first urine voided represents the contents of the anterior urethra, the second that of the posterior urethra. In reality the first portion voided washes out the discharge present in both the anterior and posterior urethra. In acute anterior urethritis pus forms only in the anterior urethra. In acute anteroposterior urethritis, pus, in addition, accumulates in the deep urethra and becomes mixed with the bladder urine and makes it turbid. Therefore, in all acute urethral inflammations, if the first portion voided is cloudy and the second portion is clear, it is reasonable to assume that the inflammation is confined to the anterior urethra only. When both urines are turbid (excluding phosphaturia) then, in all probability, anteroposterior inflammation is present. It is important to have the first portion voided a generous one, to avoid incomplete flushing out of the anterior urethra, otherwise the second urine will contain the pus left behind and incorrectly indicate posterior involvement. It will be seen from the foregoing that in *acute* urethritis the two-glass test is of most value in determining the extent of the involvement.

In subacute and chronic urethral and prostatic involvement the problem becomes more difficult, thus:

In chronic anteroposterior inflammations the amount of discharge present in the deep urethra may be so scant that none flows back into the bladder. The first portion voided is very apt to flush out the whole canal, while the second portion is clear, giving the examiner the impression that the discharge comes only from the anterior urethra, which is wrong. In these cases, where pus formation is scanty, the so-called "comma shred," which is derived from the opening of the prostatic ducts, will often help the surgeon to localize the lesion. These shreds are usually most abundant in the first specimen, and if the second urine is looked at when freshly voided, a number of them will invariably be found.

From the foregoing we have seen that these tests are not exact. A great many other "glass tests" have been devised, involving the use of three, five, seven and even nine glasses, in an attempt to localize the inflammation in the anterior and posterior urethra and prostate and vesicles exclusively. Experience has shown that this multiplicity of glass tests is of no practical value. In chronic cases, where the discharge consists only of shred formation, and where doubt exists as to their source, the following method is of value.

The patient is told to report with a full bladder. He is placed on the treatment table and the anterior urethra is flushed out with one quart of sterile water. This is collected in a basin and labeled "Specimen No. 1."

He then voids part of his urine in a cylinder which is labeled "No. 2."

The prostate and vesicles are gently and thoroughly massaged and the patient passes the remainder of the urine into another cylinder, "Specimen No. 3."

We now have three specimens for comparison.

Specimen No. 1 represents the washings from the anterior urethra.

Specimen No. 2 is the bladder urine plus the contents of the posterior urethra.

Specimen No. 3 is bladder urine plus massage products from the prostate and seminal vesicles.

Significance of Urinary Shreds.—In acute urethral inflammation when pus is produced in large quantities the urine is turbid, and contains no shreds. As the inflammation subsides and tends to become localized, an exudate forms over the involved areas but not in sufficient amount to appear at the meatus as a discharge. When washed away by the urine it appears as shreds. These consist of mucus, pus and epithelium and may or may not contain bacteria.

When shreds sink rapidly to the bottom of the cylinder they consist mostly of pus. Lighter shreds which float about and sink slowly consist mostly of mucus or epithelium. In cases treated for a long time with some of the organic silver salts, notably protargol, characteristic heavy, thick, granular shreds, yellow in color, are found. They may appear in the course of treatment after the urine has been clear. Their presence does not indicate that the case is relapsing. Stopping the injections causes their disappearance from the urine in two or three days.

The older writers laid stress upon the size and shape of urethral shreds as indicating the part of the urethra from which they were derived. Experience has shown this view to be incorrect. There is one exception, however. In chronic inflammations of the deep urethra and prostate, a small, fine, light shred is seen, having the shape of a "comma." When this type of shred is found in either the *first* or *second* urines, it invariably indicates a chronic inflammatory process in the prostatic urethra.

Generally speaking, the following conclusion may be drawn:

(1) Shreds do not necessarily indicate gonorrhea. They are frequently found in the urine of men who never had gonorrhea.

(2) Shreds mean localized areas of urethral inflammation.

(3) With the exception of the comma shred, the size and shape of shreds do not indicate what part of the urethra they come from.

Urethral Examination (*The Patient Lying on the Table.*)—The urethra is first palpated by holding the penis in one hand and palpating the outside of the canal with the thumb and forefinger of the other. In this way follicular induration, periurethral abscess, scar tissue or a foreign body in the canal may be detected.

The canal is then examined for infiltrates and stricture. *No instrument should be passed when the urethra is acutely inflamed.* Examinations should be deferred until the local symptoms have subsided. This applies, especially, to *primary acute gonorrheal urethritis and also to acute exacerbations of chronic urethritis.* In chronic relapsing cases when there is much pus, even when it is definitely known that stricture is present, this part of the examination should always be deferred until all acute symptoms have been cleared up. If this rule is adhered to, the management of this especially difficult group of cases will be remarkably free from troublesome complications.

Examination for Stricture.—The meatus is first sponged with some antiseptic solution (bichlorid 1-2000, hydrargoxycyanid 1-1000). A metallic bougie-à-boule is dipped into sterile glycerin and inserted through the meatus into the urethra, down to the "cut off" muscle. We generally begin with a No. 25 French bougie. If it enters easily, we go up the scale until we find the largest that the meatus will admit. In case 25 French does not enter, we take up the smaller ones until we find one that will pass through easily. The size of the meatus and the location and size of any narrowings are noted. Local points of tenderness encountered during the passage of the instrument are also registered. A sound corresponding in size to the largest bougie-à-boule is then passed through the urethra into the bladder, and the degree of tenderness of the deep urethra noted.

Urethroscopy.—Urethroscopy has for its object the visual inspection of the urethra. It should never be employed in the diagnosis of acute gonorrheal infection or in any condition in which the urethra is acutely inflamed. Urethroscopic examinations should always be employed to complete the diagnosis in chronic urethral inflammation. If carefully and gently performed, we have never seen any evil effects follow. Although in the great majority of cases, very little is learned by this form of examination, valuable information is obtained often enough, at least, to make it a part of the routine examination of all chronic cases.

Various types of urethroscopes are employed. For diagnosis, the direct view irrigation urethroscope, designed by Geiringer (Fig. 1), is employed. Before examining a patient the surgeon should familiarize himself with the various parts of the instrument and their assemblage.

The patient is placed in the endoscopic position with the pelvis near the edge of the table. The urethra is anesthetized if sensitive. The examiner stands at the foot of the table facing the patient. The instrument is dipped into glycerin and gently inserted through the meatus, and passed through the urethra into the bladder. The water and current are then turned on and the examiner, seated on a stool, applies his eye to the telescope. By pulling the instrument forward, a series of images of the bladder and urethra are seen.

Having become familiar with the appearance and landmarks of the normal urethra, we will briefly study the various pathological lesions which can be seen by urethroscopy, as follows:

(1) Chronic urethritis, including stricture; (2) ulcer; (3) polypi; (4) papillomata; (5) calculi; (6) foreign bodies; (7) cysts; (8) chancre and chancroid; (9) prostatism.

(1) *Chronic Urethritis.*—In describing the appearance of the urethra in chronic urethritis we will use the classification of Oberlaender, who divided it into two stages: *first,* the stage of *soft infiltration,* consisting of a small round-cell infiltration of the submucosa; *second,* the stage of *hard infiltration,* which includes all the inflammatory changes by which the round-cell infiltration is changed into connective tissue, the final conversion resulting in stricture. This fibroid change, likewise.

affects the urethral glands and crypts. In the early stage of hard infiltration, these are inflamed and either remain open or are plugged with secretion; this, Oberlaender calls the *"glandular form."* Later on, as a result of compression by scar tissue around the glands and crypts, their ducts are closed and the glands are obliterated or converted into small oval or round cysts lying beneath the epithelium. This he calls the follicular or *"dry form."* Small irregular white or yellow patches of sclerotic scar tissue are often seen.

Chronic Posterior Urethritis.—(i) *Soft Infiltration.*—Mucous Membrane.—Dark red or bluish-red areas, slightly elevated, on the mucous membrane, denote the site of infiltrates.

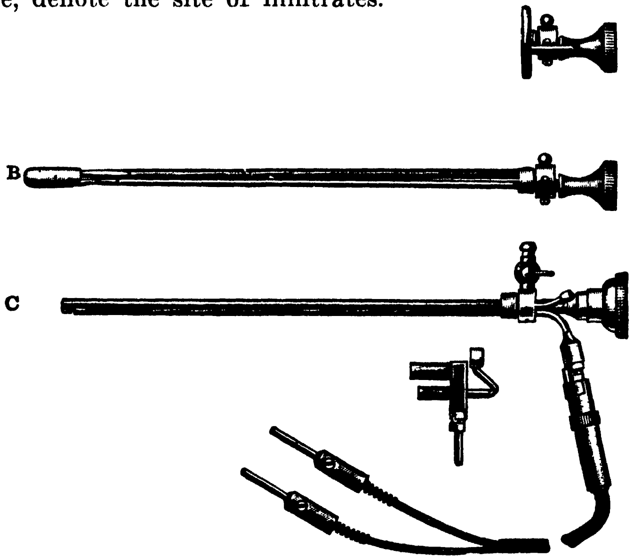


Fig. 1.—Direct-view Irrigating Urethroscope of Author for Diagnosis and Treatment

A. Sheath with movable-beak obturator.

B. Movable-beak obturator.

C. Telescope, irrigating faucet, light carrier, channel for probes, filiforms, catheter or fulgurating wire.

D. Accessory light for local applications.

Glands.—A few may occasionally be seen on the roof. The edges of ducts are thickened and surrounded by a red areola. No glandular openings are visible on the floor of the prostatic sinuses, on account of the redness and swelling of the mucous membrane.

Verumontanum.—This is dark red, swollen, and may fill the entire urethra; the surface is smooth, granular, eroded or lumpy, and bleeds easily.

(ii) *Hard Infiltration.*—(*a*) *Glandular Form.*—The mucous membrane is pale red, grayish-white or yellow.

Glands.—The mouths of the glands are gaping or plugged with secretion. The edges are swollen and are red or grayish in color.

Verumontanum.—If involved, this may show pale yellow areas; the shape is flattened or distorted.

(*b*) *Dry or Follicular Form.*—Mucous Membrane.—These are yellowish-white with pale, smooth, sclerotic areas.

Glands.—The ducts are rarely seen. One may see depressed scars, or occasionally, cystic formations (elevated yellowish or grayish-white bodies). In one case of urethritis cystica chronica, the side walls of the urethra were studded with innumerable small cysts. Occasionally single larger cysts are seen having an opalescent milky appearance.

Chronic Anterior Urethritis.—(i) *Soft Infiltration.*—Mucous Membrane.—There are hyperemic areas surrounded by healthy mucous membrane. Erosions are sometimes seen. Granular patches are found on the floor of the bulbous urethra. Thickening is shown by large puffy folds projecting upward into the field. The lumen is gaping or closed, having an irregular crescentic appearance.

Glands.—The crypts and glandular openings are not seen if embedded in the hyperemic areas. Those in the paler areas appear as red elevations discharging pus.

(ii) *Hard Infiltration.*—(*a*) *Glandular Form.*—Mucous Membrane. —The mucous membrane is paler in color; the surface appears uneven.

Glands.—The glands of Littré are surrounded by a red areola. The openings are enlarged, crater-like or plugged with secretion. The crypts of Morgagni are swollen and gaping, discharging a mucopurulent secretion.

(*b*) *Dry or Follicular Form.*—Mucous Membrane.—Diseased areas of the mucous membrane are grayish or yellowish white.

Glands.—Very few glands are seen. This is very characteristic of the dry stage, the glands and crypts being obliterated or converted into subepithelial cysts. Very frequently, both glandular and dry forms are seen in the same urethra. This Oberlaender calls "mixed infiltration."

Subacute Anterior Urethritis.—The *mucous membrane* is red and velvety. The vascular streaks are lost. The mucosa is thrown into thickened folds. The openings of the glands and crypts are red, swollen, and exude pus.

Subacute Posterior Urethritis.—The *mucous membrane* is dark, red and swollen and sometimes eroded. Occasionally follicular abscesses are seen as small yellowish elevations. The verumontanum is red and swollen.

(2) *Ulcers.*—Ulcers are usually of traumatic origin, resulting from instrumentation. They may, however, be tuberculous. They are most frequently found in the floor of the bulbous urethra. Their borders are irregular with red or grayish necrotic bases.

(3) *Polypi.*—Polypi are seen most frequently in the anterior urethra. They appear as smooth, oval, pedunculated bodies, varying from pale pink to dark red in color.

(4) *Papillomata.*—Two varieties of papillomata are seen in the urethra: (1) *flagellated;* (2) *flat sessile.* The first variety is found most frequently in the deep urethra on or near the sphincteric margin,

or springing from the colliculus. The sessile tumors have a raspberry appearance. They occur most frequently in the anterior urethra just within the meatus. In one case of chronic urethritis complicated by a congenitally contracted hypospadiac meatus, the first half inch of the urethra was almost occluded by these growths.

(5) *Calculi.*—Calculi found lying in the urethra are nearly always of renal origin. Having been passed into the bladder and, after a varying period, having entered the urethra, they are passed through it or caught at some narrow point of the canal. They are found most frequently in the prostatic or bulbous urethra or in the fossa navicularis when the meatus is small. In Guiteras' case, there were four stones found in the pendulous urethra. O'Crowley has reported one in which the bulbous and prostatic portions of the urethra were distended with calculi.

Calculi sometimes originate in the parenchyma of the prostate; these gradually enlarge and, if near the urethral mucosa, break through and are either passed or are caught and require removal. Sometimes the prostatic stone is quite large and remains firmly imbedded in the prostatic tissue and, gradually increasing in size, may break through the urethra; further deposition of salts causes the urethral portion to enlarge, the stone then having an hour-glass or dumb-bell shape.

(6) *Foreign bodies* are rarely found in the male urethra. Bits of catheter, pencils, and pen holders have, however, been reported.

(7) *Solitary cysts* of non-infectious origin are seen but rarely. They have been seen in the deep urethra near the sphincteric margin.

(8) *Chancre and chancroid* of the urethra occur most frequently just within the meatus and can usually be seen without the aid of the urethroscope.

(9) *Prostatic Hypertrophy.*—That portion of the posterior urethra, lying between the verumontanum and vesical sphincter, normally has a cylindrical appearance. In beginning hypertrophy, its transverse diameter becomes narrowed, due to the projection of the enlarged lateral lobes of the prostate into the urethra. In advanced hypertrophy, this narrowing becomes more marked, giving the urethra the appearance of a vertical slit, slightly wider near the urethral floor. The internal vesical sphincter, instead of being round, assumes the same shape.

TREATMENT OF ACUTE GONOCOCCAL URETHRITIS

The treatment of gonococcal urethritis is systemic and local. The former comprises dietetic and hygienic measures, and also the internal administration of curative remedies. The latter deals with the local applications of drugs to the affected parts.

Before taking up the detailed study or consideration of the treatment of gonorrheal infections we will describe the various internal remedies and the drugs employed locally.

I. **Internal Remedies.**—The number of drugs employed in the internal treatment of gonorrhea is legion. This method of treatment is still

Practice of Medicine—Tice.

☛ These new pages 477–482 take the place of the old pages 477–482, Vol. III. Take out the

The internal remedies which enjoy most favor at present are **sandalwood oil, copaiba, cubebs, kava-kava, buchu, methylene blue** and the **urinary antiseptics.**

Sandalwood oil (oleum santalis) is a pale yellow oil distilled from the wood of East Indian *Santalum album.* The dose is 10 to 30 minims (0.6 to 2.0 c.c.) three times a day, three hours after eating, in capsules or emulsion. In some patients, even a small dose of sandalwood oil is irritating to the digestive tract, or it may cause distressing pain in the back, which calls for a diminution in dose or a change of the drug.

Copaiba is a fluid oleoresin obtained from the trunk of a certain species of *Copaifera.* The dose is ½ to 1 dram (2.0 to 4.0 c.c.) in capsules or emulsion. In larger doses or after continued use it is apt to produce indigestion and diarrhea. It occasionally produces an erythema or urticarial eruption.

Cubeb is the dried unripe fruit of *Piper cubeba.* It is less unpleasant to the palate than copaiba and less liable to upset the digestion. In large doses it sometimes irritates the bladder. It is frequently prescribed with copaiba either in pill or emulsion. The dose of the powder is 30 to 60 grains (1.95 to 3.90 grams), fluid extract ½ to 1 dram (2.0 to 4.0 c.c.), oleoresin in capsules, 0.3 to 1 c.c. (5 to 15 minims).

Kava-kava is the dried rhizome of *Piper methysticum* (Polynesia). The dose of the fluid extract is 30 to 60 minims (1.9 to 3.8 c.c.). Its action is similar to the other balsamics, but it has in addition an anesthetic effect on inflamed mucous membranes.

Wintergreen oil is of service when the balsamics disagree. The dose is ten minims in capsule, three times a day.

Methylene blue is seldom employed.

Urinary antiseptics, such as **hexamethylenetetramin, salol, benzoates** or **benzoic acid, boric acid, borates** and **methylene blue,** have no appreciable therapeutic effect upon urethral inflammation. These substances, which are of such great value in all urinary suppurative conditions located in the upper urinary tract, are useless below that point. They are useful to protect the kidneys and should be given whenever an unusual rise in temperature occurs during the course of a gonorrhea. Hexamethylenetetramin, commonly known as **urotropin,** is the drug of choice. Its antiseptic action depends upon its power of liberating formaldehyd in the urine. It acts only in acid urine and should never be prescribed with alkalies. The urine must be tested in every case and if found to be neutral or alkaline, an attempt should be made to alter its reaction by administering **sodium benzoate** 15 to 20 grains (1.0 to 1.3 grams), or the **acid phosphate of sodium** 30 to 60 grains (1.9 to 3.8 grams), twice daily.

The following combinations have been employed in the routine treatment of urethral inflammation:

(1) *Oleum Santali Emulsion.*

℞

Olei santali	f ℥i (30.0 c.c.)
Potassii citratis	℥i (31.1 grams)
Syrupi simplicis Mucil. acaciæ Aquæ gaultheriæ	āā q.s. ad ℥iv (120.0 c.c.)

M. Ft. Emuls.
Sig.: ʒi t.i.d. 2 h. p. c.

(2) *Lafayette Mixture.*

℞

Copaibæ Spiritus etheris nitrosi Spiritus lavandulæ	āā ℥ss (15.0 c.c.)
Liquoris potassii (U. S. P.)	ʒi (4.0 c.c.)
Syrupi simplicis Mucilagis acaciæ Aquæ gaultheriæ	āā q.s. ad ℥iv (120.0 c.c.)

M. Sig.: ʒii t.i.d. p.c.

Of the foregoing combinations, the writers prefer **sandalwood** oil, either alone in capsules, ♏ x four times a day, or combined with **citrate of potash** in emulsion. A very good preparation of the oil in combination with **kava-kava** is prepared under the proprietary name of **Gonosan.** The dose is 6 to 8 capsules during the day.

II. **Local Treatment of Urethritis.**—Before considering the detailed treatment of acute and chronic urethritis, the physician should familiarize himself with the drugs employed and the various methods of applying them to the urethra.

Drugs.—The list of drugs which have been used in the local treatment of gonorrheal urethritis is a long one. The following table includes only those in general use and many old-time favorites are excluded. New preparations are being constantly proposed, which proves that perfection in urethral medication has not yet been attained.

The following list represents the solutions usually employed, the form in which they are most conveniently kept, and the strengths in which they are employed either for hand injection by the patient, irrigation or instillation.

Name	Form	Hand Injection	Irrigation	Instillation
Silver nitrate	50 per cent. solution		1:6000–1:1000	0.5–5 per cent.
Protargol	5 grain powders	0.25–1 per cent.	0.1–0.5 per cent.	1–5 per cent.
Argyrol	Crystals	5–20 per cent.		10–25 per cent.
Albargin	0.2 gram tablets	0.1–1 per cent.	0.05–0 02 per cent.	1–5 per cent.
Novargon	Crystals	1:500–1:50	1:3000–1:1000	1:20–1:10
Potassium permanganate	1 grain tablets		0.01–0.05 per cent.	
Hydrargyrum oxycyanid.	0.25 gram powders		0 01–0.05 per cent.	
Copper sulphate	10 per cent. solution		1:500–1:250	
Zinc sulphate	5 per cent. solution	0.25–0.5 per cent.	0.1–0.5 per cent.	
Zinc sulphocarbolate	Powder	1:500–1:200		
Zinc acetate	See text	1:500–1:100		
Vegetable astringents	See text			
Ointments and bougies	See text			

The drugs in the foregoing table may be roughly divided into **antiseptics, astringents, sedatives** and **stimulants.** Most of them exhibit two or more of these functions, either of which will dominate according to the concentration employed. Thus the organic silver salts are essentially antiseptics. **Argyrol** in strengths up to 15 per cent. is sedative, while stronger solutions (25–50 per cent.) are antiseptic, stimulating and also astringent. **Protargol** is antiseptic and astringent. **Silver nitrate** in weak solutions (1–4000) is antiseptic, astringent and mildly stimulating; in 1 per cent. strength, its chief action is astringent, while higher concentrations have caustic properties. **Zinc sulphate** and **acetate** are used only for their astringent properties.

Vegetable astringents, notably **hydrastis,** formerly enjoyed much favor. If used at all, they should only be employed as injections in nongonorrheal urethritis as substitutes for the zinc salts. Personally, we find them of little or no value.

The application of **ointments, oily preparations** and **soluble bougies** containing one or more antiseptic or astringent drugs, still appeals to some. The authors prefer the injection of watery solutions.

The physician should select a few of these drugs and learn thoroughly their dosage, action and mode of administration. *It is better to have a complete working knowledge of a few preparations than a hazy appreciation of a large number.*

Of the many new preparations for the local treatment of gonorrhea which have appeared in recent years, only two have proven themselves worthy. These are **mercurochrome** *and* **acriflavine.**

Mercurochrome—220 contains 23–24 per cent. mercury in molecular combination with the dye eosin. In this form the mercury, while retaining its germicidal power, is not precipitated by proteins or alkalies. Young recommends its use as follows:

In Anterior Urethritis.—Solutions ranging from one quarter to one per cent. are injected every three or four hours, the weaker solutions being used in the hyperacute cases. A preliminary irrigation of the anterior urethra with sterile water or normal saline is essential.

In Posterior Urethritis.—First irrigate with sterile water or normal saline to remove mucus and pus. Inject one half to one ounce of a one per cent. solution of mercurochrome by means of a posterior urethral syringe or catheter.

☛ These new pages 477–482 take the place of the old pages 477–482, Vol. III. Take out the old, insert the new.
Practice of Medicine—Tice.

In Female Gonorrhea.—Hager and von Lackum of the Mayo Clinic recommend the use of mercurochrome, alternating with silver compounds and iodine. During the acute stage, they swab the cervix and vault with tincture of iodine or a 2 per cent. solution of silver nitrate. This produces a profuse desquamation and discharge. The vagina is then wiped dry, and pure crystals of mercurochrome are placed in the cervix. The vault is swabbed out with one per cent. mercurochrome.

In Vulvovaginitis a one per cent. mercurochrome ointment is daily injected into the vagina.

In Ophthalmia Neonatorum Clapp and Martin employ frequent instillations of a two per cent. solution in the eye.

Acriflavine is an antiseptic dye. For urethral injections the strength of the solution used is from 1–5000 to 1–3000. The injections are given three times a day, holding in the fluid for five minutes.

Comparative Value of Local Remedies.—Just as in other obstinate conditions, there is a diversity of opinion regarding the relative merits of the various local remedies employed. Differences of opinion exist among urologists as to the relative values of the organic silver salts. This confusion is added to by the manufacturers, each of whom extols the value of his own preparation.

Much work has been done in the laboratory and upon animals to test the value of various drugs. Thus Marshall and Neave found that, whereas the majority of silver salts were powerfully bactericidal upon the *Staphylococcus pyogenes aureus,* argyrol showed no such effect.

According to Cragin, argyrol in 20 per cent. strength destroys the gonococcus in 20 seconds, but is inefficient with streptococci and *Staphylococcus pyogenes aureus.* Burnett, in his experiments, showed that neither argyrol nor silver nitrate showed any power to penetrate the urethral mucous membrane.

From the foregoing, the impracticability of classifying these salts by laboratory or test-tube standards becomes evident. Clinical experience is the only criterion, and it has shown that the **organic silver salts** are the best remedies in acute gonococcal inflammations, by virtue of their being bactericidal and relatively non-irritating. In chronic gonorrhea they are useful only when the urethra is very sensitive and irritable to silver nitrate, which is the remedy of choice.

Personally, we find **argyrol, protargol** and **silver nitrate** the most efficient in the routine treatment of acute and chronic urethritis. We have practically discarded the use of **potassium permanganate,** finding it inferior to either protargol or argyrol. Although it apparently seems to hasten the cure by diminishing the discharge more quickly than the silver salts, it gives the physician and patient a sense of false security as to the progress of the case. Discontinuing the injections frequently causes the prompt reappearance of the discharge, very often to the bewilderment of the physician and the discouragement of the patient.

Therapeutic Value of Mercurochrome and Acriflavine.—Clinical experience has shown that these drugs are valuable adjuvants in the treatment of gonorrhea. In our experience they rank about the same as protargol and argyrol. The practitioner must not, however, rely solely upon either of them in treating all cases, otherwise he will meet with

Practice of Medicine—Tice.

☛ These new pages 477–482 take the place of the old pages 477–482, Vol. III. Take out the old, insert the new.

many failures. Best results are obtained when they are employed alternately with the silver salts. Used in this way, there is no danger of the gonococcus developing a tolerance for or a resistance to any particular drug.

Mercurochrome is objectionable for home treatment because of its intense staining qualities. For this reason we use it only in the office. When we first started to use it, we found that it proved very irritating when instilled into the deep urethra. In fact several cases developed acute prostatitis and epididymitis which we attributed to the irritating effects of the drug. At present, if we decide to employ it at all in posterior gonorrhea we first administer a course of the milder silver salts, in order to determine the tolerance of the deep urethra to treatment. In the treatment of periurethral abscess and sinuses mercurochrome is more effective than acriflavine and the silver salts.

Astringent injections of **zinc** and **alum** are of no value in gonococcal urethritis. They are but little used except in controlling the discharge in chronic anterior urethritis until more efficacious local treatments effect a cure.

METHODS OF ADMINISTRATION.—The application of remedial agents to the urethra is performed in the following ways: (1) Injection with a small syringe. (2) Irrigation with (*a*) large piston syringe, (*b*) irrigating jar. (3) Instillation. (4) Urethroscopic application.

The patient should empty his bladder immediately before any treatment is applied to the urethra, thereby washing out any discharge which may be present and also enabling the surgeon to note the progress of the case by the appearance of the urine.

(1) *Injection with a Small Syringe.*—These are generally applied by the patient himself. He is instructed to provide himself with a two-dram glass or hard rubber syringe having *a blunt tip*. The tip may also be of soft rubber. The syringe is filled and applied snugly within the meatus, aided by lateral pressure applied with the thumb and forefinger of the left hand. The injection is made slowly and there is no need for the patient to press against the urethra to prevent the solution from entering the bulbous urethra.

In acute gonorrhea, the injection is made three or four times a day. In chronic gonorrhea, not oftener than twice a day. The solutions usually employed are: protargol 1/4 to 1/2 per cent., argyrol 10 to 20 per cent.

(2) *Irrigation.*—This is accomplished either with a large piston syringe of the Janet-Frank type (Fig. 2), or with an irrigating jar suspended from the wall. The nozzle of the syringe should be blunt-tipped. This method has for its object the flushing out of the anterior and also of the posterior urethra. The nozzle is pressed against the meatus and enough fluid injected to distend the urethra, after which the fluid is allowed to flow out. This intermittent irrigation is continued until the syringe is emptied. In order to irrigate the deep urethra and bladder, the nozzle is held firmly against the meatus and the fluid slowly injected. To relax the sphincter muscle, the patient is instructed to breathe deeply or to attempt to urinate. Usually, after a few minutes, the "cut-off" muscle relaxes and the solution flows through the deep

urethra into the bladder. When enough of the solution has been passed the patient empties his bladder, thus securing a two-way irrigation.

The authors find this method a cumbersome one and very tiring if many patients are to be treated. The irrigating jar will be found much more convenient. The apparatus consists of a one-quart jar suspended from the wall about 3 to 5 feet above the level of the table. About 5 feet of rubber tubing is attached to the jar.

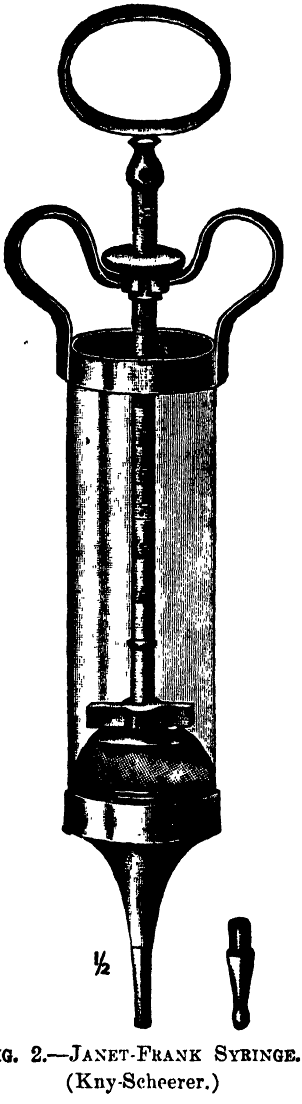


Fig. 2.—Janet-Frank Syringe. (Kny-Scheerer.)

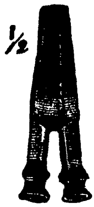


Fig. 3.—Chetwood's Irrigating Nozzle. (Kny-Scheerer.)

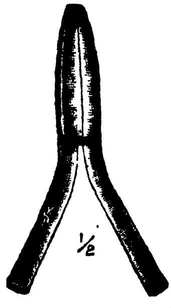


Fig. 4.—Kiefer's Irrigating Nozzle. (Kny-Scheerer.)

Various nozzles are employed (Figs. 3 and 4). The Chetwood scissors and two-ways glass nozzle for irrigating the anterior urethra, the Swinbourne cut-off and shield and the Janet nozzles are recommended.

The irrigation of the anterior or posterior urethra is performed in the same manner as with the piston syringe.

Instead of employing hydrostatic pressure to relax the cut-off muscle when the deep urethra and bladder are irrigated, catheter irrigation may be used. The technic is as follows: A straight soft rubber 12-14 Fr. catheter is lubricated either with glycerin or other lubricating jelly. The catheter is then introduced into the bladder. The irrigating jar is connected with the catheter by means of a fine-pointed nozzle. About two ounces of the solution are allowed to flow into the bladder. The catheter is then disconnected from the jar, and as the solution flows out of the bladder, through the catheter, the latter is gently withdrawn about 3 to 4 cm. until the flow stops, which shows that the eye of the catheter lies within the prostatic urethra. The catheter is again connected with the irrigating jar, and the solution flows into the catheter, through the prostatic urethra into the bladder. When the patient feels a desire to urinate, the flow is stopped and the catheter withdrawn. The patient gets off the table and empties his bladder.

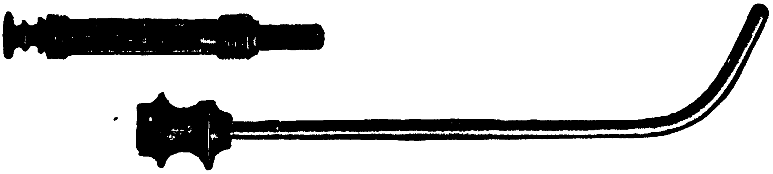


FIG. 5.—ULTZMANN'S INSTILLATION SYRINGE. (Kny-Scheerer.)

The authors prefer the irrigation of the deep urethra with a catheter. It is much more convenient and less trying to the patient, unless he can easily voluntarily relax the sphincter muscles. In nervous patients, it is sometimes at first impossible to pass a soft catheter into the bladder, owing to spasm of the "cut-off" muscle, in which case a woven coudé catheter should be used.

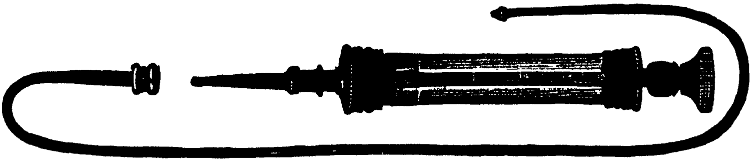


FIG. 6.—GUYON INSTILLATION SYRINGE. (Kny-Scheerer.)

(3) *Instillations.*—The object of instillation is to place upon a given portion of the urethra a few drops of a concentrated solution. The instillator (Figs. 5 and 6) consists of a syringe barrel to which is attached a hollow metal catheter, as in the Ultzmann or Keyes instrument, or a woven catheter of the Guyon type. The authors prefer the Ultzmann instillator. The metal catheter portion of the instrument is made either of steel or silver. The former, owing to oxidation, becomes clogged up, whereas the silver catheter always remains patent.

Inasmuch as instillations are nearly always made in the deep urethra, the surgeon should have a clear idea of the precise position of the instrument when it passes the external sphincter. Usually, a distinct "jump" is felt as it passes over the "cut-off" muscle. In case of doubt we may always feel certain that the point of the instrument is in the deep urethra when its shaft rests without support at an angle of 45 degrees to the horizon.

(4) *Urethroscopic Applications.*—These are considered under chronic urethritis.

III. **Routine Treatment of Acute Gonorrheal Urethritis.**—ACUTE ANTERIOR URETHRITIS.—The intensity of the inflammation may vary within wide limits. In some, which for convenience may be termed *hyperacute,* the local reaction is very intense, characterized by marked swelling and eversion of the meatus, swelling and redness of the glans and prepuce, profuse greenish-yellow purulent discharge, which may be blood streaked, and intense burning on urination. In others, which may be called moderately severe or *acute* cases, the local signs are much less marked. It is important to consider the intensity of the inflammation when beginning the treatment, because if injections are started too soon in the hyperacute type, the symptoms are aggravated, frequently causing an extension into the deep urethra and prostate.

When a patient with acute urethritis presents himself for treatment, he is examined as previously described. When the diagnosis of acute anterior gonorrhea has been made, the patient is given instructions regarding cleanliness, diet, rest and sexual hygiene.

Cleanliness.—The parts should be washed as often as necessary with soap and water. The discharge should be collected in a small gauze bag which is tied around the waist and in which the penis is placed. A number of these are on the market. If the prepuce is long, the glans penis may be thrust through a slit in the center of a square piece of gauze, over which the foreskin is then drawn.

The patient is advised to wear a jock strap as a preventive of epididymitis. This, incidentally, serves to hold the cotton or gauze covering the glans. Packing the prepuce with gauze is a bad practice because it prevents proper drainage. The patient is warned of the danger to his eyes from contamination with gonorrheal pus. He is told to thoroughly wash his hands with soap and water every time he touches his penis.

Diet.—Meat in excess, highly seasoned or salty foods, sauces, condiments, strong tea or coffee, pickles, tomatoes and asparagus, should be avoided. Alcohol, ale, beer, cider and ginger ale are not allowed. Keyes' rule, that any substance which burns the palate as it enters the body will burn the urethra as it issues forth (chemical not physical heat is meant), is a good one.

Water.—About eight glasses of water should be drunk during the day. Sparkling water or French Vichy may be used.

Rest.—Patients are instructed to take as much rest as possible. It is better to ride than to walk and to sit rather than to stand. The shaking and jolting in railway trains and automobiles seems particularly injurious.

Sexual Hygiene.—Sexual intercourse must not be indulged in until the disease is cured. Anything liable to induce sexual excitement, such as association with women, suggestive literature and pictures, should be avoided, otherwise the resulting congestion of the deep urethra and prostate favors the extension of the inflammation into these organs.

Internal Medication.—The **sandalwood oil emulsion** (*see* p. 478) is given as long as there is a free urethral discharge. When the discharge is scanty and has changed from frank pus to a thin grayish mucus, there is nothing to be gained by giving the balsamics or, in fact, any other urinary antiseptics. The best guide is the appearance of the urine. So long as the urine is turbid (due to pus) sandalwood oil alone or in combination is kept up, provided it does not upset the digestion too much. If the patient objects to the taste of the emulsion, which is very disagreeable, sandalwood oil may be given in 10 minim capsules, one capsule three times a day after meals and on retiring. The authors prefer **gonosan** capsules; dosage, two capsules four times a day. Some patients tolerate the oil better on an empty stomach. Others do better when it is taken one hour after meals.

In moderately severe cases, the patient can at once be placed on a hand injection of 1/4 per cent. **protargol.** The injection is made four times a day and retained for five minutes each time. Soaking the penis in hot water seems to intensify the action of the injection and to moderate the pain. Ten per cent. **argyrol** may be used instead. This is so messy, owing to its deep color, that protargol is preferable. As a rule, the pain caused by protargol in this strength lasts but a few moments and is readily borne. After three or four days, the strength of the injections can safely be raised to 1/2 per cent. If it produces severe or lasting pain it should be reduced to the former strength. Some urologists employ protargol up to 2 per cent. Our own experience has taught us that nothing is gained by these higher concentrations in acute urethritis. One per cent. may be employed. Usually, however, it causes irritation.

In hyperacute cases, injections are not begun until the local symptoms subside. This may be hastened by prolonged soaking of the penis in hot water. When the authors consider that the case is ready for local treatment, they inject one dram of 15 per cent. argyrol into the anterior urethra. This is retained for five minutes. This is repeated on the following day and if no irritation is produced the patient is instructed how to inject himself with the protargol solution. *The silver salts are employed as long as gonococci are present in the discharge or urine.*

When the gonococci can no longer be demonstrated, it is still the custom of many to employ an **astringent injection** of the following type:

℞

Aluminis	āā grains vi-xii	(0.4-0.8 gram)
Zinci sulphatis		
Phenol		
Glycerini	℥ss	(15.0 c.c.)
Aquæ destillatæ	ad ℥iv	(120.0 c.c.)

M. Sig.: Inject b.i.d.

The authors do not employ them, however, relying upon the astringent properties of **silver nitrate.**

Office Treatment.—The duration of the disease may be shortened by treatment in the office. Flushing the urethra with **warm protargol solution** ⅛ to ¼ per cent., temperature 100°-105° F. (37.8°-40.6° C.), materially hastens the disappearance of the discharge. This is performed once a day, until the discharge shows signs of letting up, when every other day will be sufficient.

Protargol irrigations are kept up as long as the urine is cloudy, due to pus.

When the urine is almost clear and contains shreds, then **silver nitrate** is the drug of choice. In weak solutions, its action is antiseptic and astringent.

We begin with a 1-8000 solution, and gradually increase in strength, rarely exceeding 1-1000. The **irrigations** are preferably made with an irrigating jar suspended about three feet above the level of the table. Irrigations are given on alternate days. **Distilled water** is preferable to tap water. The temperature of the water should be from 100°-105° F. The authors employ a stock solution of silver nitrate 100 per cent. strength for making dilutions. Two drops of this solution added to 1 quart of water make approximately 1-800 dilution.

The following table for increasing the strengths of silver nitrate solutions in both acute and chronic urethritis will be found useful:

1st	day,	2	drops	100	per	cent.	$AgNO_3$	Solution	= 1-8000	approximately
3d	‘‘	3	‘‘	‘‘	‘‘	‘‘	‘‘	‘‘	= 1-6000	‘‘
5th	‘‘	4	‘‘	‘‘	‘‘	‘‘	‘‘	‘‘	= 1-4000	‘‘
7th	‘‘	5	‘‘	‘‘	‘‘	‘‘	‘‘	‘‘	= 1-3200	‘‘
9th	‘‘	6	‘‘	‘‘	‘‘	‘‘	‘‘	‘‘	= 1-2800	‘‘
11th	‘‘	7	‘‘	‘‘	‘‘	‘‘	‘‘	‘‘	= 1-2300	‘‘
13th	‘‘	8	‘‘	‘‘	‘‘	‘‘	‘‘	‘‘	= 1-2000, etc.	

From the foregoing table it will be seen that the strength of the solution is increased one grain to the quart each time.

If at any time the silver nitrate causes irritation, evidenced by increased pain following administration, weaker dilutions must be used. *If used with judgment and proper strengths in the subsiding stages of the inflammation, better results will be obtained with silver nitrate irrigations than with any other preparation. If on the other hand it is employed in the acute stage or in strong solutions, only harm will result. Furthermore, the patient should never be allowed to use the nitrate for hand injections.*

Frequently when employed in concentrations over 1-2000, a discharge may appear within a few hours, or the patient may notice it the following morning. Unless the solution is too strong, this discharge usually disappears promptly in the first twelve hours following irrigation and is of no significance. *In all events, the irrigation must not be repeated until all signs of local reaction have disappeared.*

During the course of the disease certain symptoms call for special attention, such as:

Chordee.—This distressing symptom can often be prevented by **prolonged soaking of the penis in hot water** before retiring and the internal administration of the following:

℞

Sodii bromidi	℥i	(31.1 grams)
Hyoscyaminæ hydrobromidi	grain ¼	(0.016 gram)
Aquæ menthæ piperitæ	ad ℥iv	(120.0 c.c.)

M. Sig.: ʒi on retiring, to be repeated once during the night.

Lupulin grains xxx-xl (2.0-2.6 grams) at bed time, **monobromid of camphor** grains v (0.3 gram) are sometimes effective. In specially severe cases the following **rectal suppositories** may be used, but with caution:

℞

Morphinæ sulphatis	grain ¼	(0.016 gram)
Quininæ sulphatis	grains x	(0.65 gram)
Olei theobromatis	q.s.	

M. Ft. Rectal Suppository.

Sig.: Insert one at bed time.

The patient should be instructed to **lie on his side.** The time-honored method of tying a towel around his waist with the knot in the back may assist him in this.

Ice water is useful when the penis is erect and in chordee. The patient usually urinates if he can and then by immersing the penis in cold water, he usually succeeds in reducing the erection. Slowly bending the rigid member downward and retaining it between the thighs often helps.

Severe Burning on Urination.—This symptom rarely calls for special attention in acute anterior urethritis. Diluting the urine by **drinking freely of water** usually moderates it. In severe cases the following mixture is useful:

℞

Liquoris potassii (U. S. P.)	℥i	(30.0 c.c.)
Tincturæ hyoscyami	℥i	(30.0 c.c.)
Syrupi cinnamomi	ad ℥iv	(120.0 c.c.)

M. Sig.: ʒi in glass of water 2 h. p. c.

Under the foregoing methodic treatment, favorable cases clear up in from six to eight weeks. The reader is referred to p. 512 for the various tests employed to determine whether the patient is cured.

ACUTE POSTERIOR URETHRITIS.—When gonorrheal inflammation involves the deep urethra, there is always some involvement of the prostate gland. The degree of prostatic inflammation may be so slight that there is no apparent change which can be detected, or the entire gland may be involved. Under this title we will consider the treatment of posterior urethritis unaccompanied by any palpable change in the prostate.

During the treatment of acute anterior urethritis the urine voided in two glasses should be examined at each visit. The appearance of pus in the second glass denotes invasion of the posterior urethra.

Local treatment of the posterior urethra will depend upon:

(1) Intensity of the inflammation in the anterior urethra.
(2) Intensity of the inflammation in the deep urethra.

This brings the following types of cases up for consideration:

(1) When the inflammation in the anterior urethra is very severe, no local treatment is applied to the posterior urethritis.

(2) When the anterior urethritis is moderately severe and under control, treatment of the posterior urethra can be begun at once, except in the case mentioned under (3).

(3) When the posterior urethritis is very severe, as shown by subjective symptoms of painful and frequent urination, tenesmus, etc., the physician can begin local treatment at once or wait until the severity of the symptoms subsides.

The type of treatment will depend upon the experience of the physician and the previous history of the patient. If pains and frequency increase or do not diminish under local treatment, it should be discontinued. *When in doubt stop all local treatment.*

Treatment of the posterior involvement is usually begun with **instillation of argyrol** 15 per cent. once or twice a day. If well tolerated 25 per cent. argyrol is used. The patient at the same time keeps up the hand injections for the anterior urethra. The argyrol treatment is kept up until all subjective symptoms disappear and the second urine becomes clear. If the second urine still contains pus, or shreds persist, **catheter irrigations of silver nitrate** beginning with 1:8000 and cautiously increased in strength are employed.

When the anterior inflammation is very acute, all local treatment is stopped. **Sandalwood oil** is administered internally (see anterior urethritis), and the patient is told to rest as much as possible. It not infrequently happens that, in the course of a few days, the second urine will clear up and no treatment of the deep urethra will be necessary. This applies only to the mild posterior involvement. If the subjective symptoms increase, the patient is put to bed, and a **hot-water bag** applied to the perineum. **Hot rectal saline injections** are given twice a day. The following formula will assist in moderating the frequency, burning and tenesmus:

℞

Kalii (potassii) acetatis	℥i	(31.1 grams)
Tincturæ belladonnæ	℥ss	(15.00 c.c.)
Aquæ menthæ piperitæ .... ad	℥iv	(120.00 c.c.)

M. Sig.: ʒi t.i.d. between meals in a glass of water.

If the pain and frequency continue to increase, **sedative suppositories** of the following type may be employed:

℞

Morphinæ sulphatis	grain ¼	(0.016 gram)
Quininæ sulphatis	grains x	(0.65 gram)
Olei theobromatis	q.s.	

M. Ft. Rectal suppositories.
To be inserted once or twice a day.

℞

Morphinæ sulphatis	grain ¼	(0.016 gram)
Antipyrinæ	grains x	(0.65 gram)
Olei theobromatis	q.s.	

M. Ft. Rectal suppositories.
To be inserted once or twice a day. These suppositories should be stopped as soon as the symptoms moderate.

Some urologists recommend in these cases the instillation of 2 or 3 drops of 5 to 10 per cent. **silver nitrate**, claiming that it often causes a marked diminution in pain. Although this procedure is of value in relieving irritability of the deep urethra, due to causes other than gonorrhea, the writers do not recommend it in acute posterior gonorrhea, on account of the possibility of setting up an acute prostatitis or epididymitis. When the symptoms have subsided, treatment of the anterior and deep urethra is continued as described above.

IV. **Prophylaxis.**—To avoid gonorrhea, the man should urinate immediately after coitus and thoroughly **wash with soap and water.** The use of a **condom** is a perfect safeguard against infection unless accidentally ruptured during coitus.

The following therapeutic measures afford a reliable means of preventing infection, if employed within 6 hours after exposure and no later than 12 hours:

(1) **Instillation** in the meatus of **25 per cent. argyrol** freshly prepared.

(2) **Injection** of **3 per cent. protargol.**

(3) **Irrigation** of the anterior urethra with 1:1000 **potassium permanganate.**

(4) *U. S. Navy Prophylaxis:* On his return from shore leave, the sailor washes his genitals with soap and water and urinates. An injection of 1 c.c. of **2 per cent. protargol** containing **15 per cent. glycerin** is retained for five minutes. To prevent syphilis, **calomel ointment** is applied to the external genitals and left on for two hours.

V. **Abortive Treatment.**—The abortive method has for its object the quick cure of a beginning gonorrhea. Many methods of treatment have been advised, some more complicated than others. The originators are very enthusiastic over the results obtained by their respective methods.

Thus Frank and Lewin report 45 per cent. cures; Bierhoff 50 per cent. To insure success treatment must be begun within a few hours after the appearance of the discharge.

It is the experience of most observers that only in exceptional cases is it possible to abort gonorrhea. Most are agreed that, although at times rapid cures are obtained in secondary gonorrhea, it is almost impossible to abort a primary attack. The authors' own experience has led them practically to give up any attempt to abort gonorrhea by any special method. They occasionally obtain quick results with the routine treatment outlined in acute anterior urethritis. At any rate, if failure results from this method, no harm has been done, as is frequently the case when strong injections are made in attempting to abort the disease in a few days.

The drugs employed are **protargol** ranging in strength from 1/6 to 4 per cent., **silver nitrate** 1 : 3000, **argyrol** 5 to 25 per cent., and **potassium permanganate** 1 : 5000 to 1 : 1000.

For the detailed description of the various methods, the reader is referred to the larger special works on this subject.

TREATMENT OF CHRONIC GONORRHEA IN THE MALE

In beginning the treatment, the question of chronicity should, for the time being, be entirely disregarded. The treatment should be palliative, along the lines described under the acute infection. When the acute process subsides, then the case should be examined for chronic foci and the proper treatment for these applied.

When a patient with chronic gonorrhea presents himself for treatment, it is essentially important for the physician to study the extent and nature of the lesions present, before outlining the treatment.

Frequently, the condition of the patient when first seen is very apt to mislead the examiner, unless a careful history is taken, and a thorough routine examination is made as described on page 469.

Chronic cases of urethral or prostatic gonorrhea, when first seen during an acute exacerbation, are especially puzzling. Thus a chronic anterior urethritis may simulate an acute anterior inflammation of recent origin. This, in turn, may invade the deep urethra and prostate, or on the other hand, a chronic prostatic gonorrhea lights up and infects the anterior urethra. In this way, an acute relapse of a chronic gonorrhea may obscure the location of chronic infected areas.

A careful history will usually not only reveal the existence of a previous infection, but also reveal certain symptoms which indicate that the patient had not been cured of previous attacks.

When there is a history of many attacks of urethritis occurring within a short space of time, it is reasonable to assume that these, so-called acute attacks of gonorrhea, are acute relapses of a chronic gonorrhea.

In all chronic cases, the physician should also remember that in the great majority, probably 85 per cent., there is an involvement of the deep urethra and prostate. Unless these cases are examined from this standpoint, many errors in diagnosis and failures in treatment will result. For therapeutic purposes, chronic gonorrhea may be classified as follows: (1) *chronic anterior gonorrhea;* (2) *chronic posterior gonorrhea;* (3) *chronic anteroposterior gonorrhea;* (4) *acute exacerbations of chronic gonorrhea.*

(1) **Chronic Anterior Gonorrhea.**—When chronic gonorrheal inflammation is present in the anterior urethra, the lesions most frequently responsible for the persistence of the infection are folliculitis and stricture. Fistulæ resulting from periurethral abscess may also be the underlying cause.

FOLLICULITIS.—This condition is readily diagnosed with the water dilatation urethroscope. The indications for *treatment* are (1) to cause absorption of the periglandular infiltrate, (2) to destroy the gonococci. The former is accomplished by **dilatation,** the latter by **antiseptics.**

If an active urethral discharge is present the patient employs a hand injection of **protargol** ½ per cent. Twice a day is sufficient. The administration of **internal urinary antiseptics** is of doubtful benefit unless acute inflammation is present, or if the urine is turbid, due to pus.

In quiescent cases, **irrigations** of the anterior urethra are given every second day. **Silver nitrate** is the remedy of choice. Weak dilutions should always be used in the beginning. It is always safe to start with 1-8000. The strength is gradually increased according to the method described on page 486. Usually the irrigations can be given every second day. They must not be repeated until the irritation (increased discharge and burning) produced by the previous treatment has subsided.

Dilatation may be performed with metal sounds or dilators. The authors prefer the dilators (Figs. 7-10). If used with gentleness, less pain is caused and higher degrees of dilatation are obtained. Local anesthesia should never be employed to lessen the pain of dilatation because extreme pain is, in itself, a contraindication to dilatation. It is essential also to have a fair-sized meatus to facilitate instrumentation. If the meatus is less than 25 French, it should be cut to admit a 31 sound.

To determine what size sound to begin with, **olivary bougies** are passed. A sound corresponding in size to the largest bougie which the urethra can readily admit, is lubricated and introduced into the urethra down to the "cut off" muscle. The urethra is then gently massaged over the sound. This assists in expressing little plugs of secretion from the mouths of the inflamed glands. Allowing the sound to remain in the urethra for 10 or 15 minutes, as was formerly the custom, is unnecessary and may cause irritation and spasm. After dilatation, the urethra is **irrigated** with the **silver nitrate solution.** At the next visit a sound one number larger is inserted. If local treatment causes a marked increase in discharge and urethral tenderness and soreness it should be discontinued until all urethral irritation has subsided. When the urethral discharge has stopped and nothing but shreds remain, the hand injection

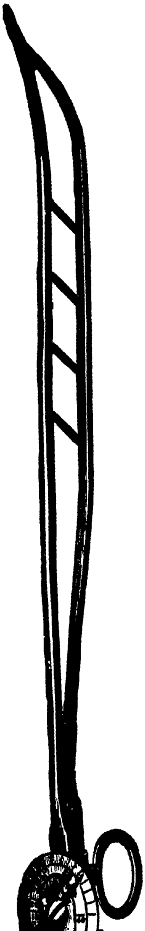


Fig. 7.—Oberländer's Anteroposterior Urethral Dilator. (Kny-Scheerer.)

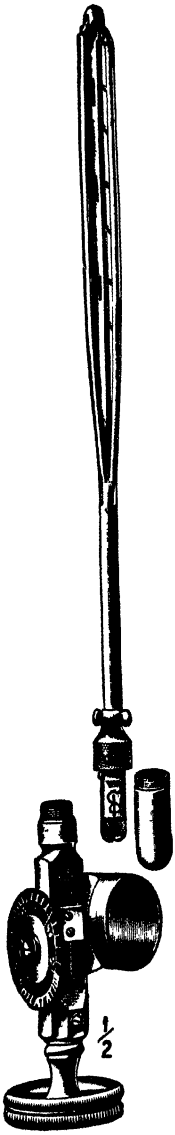


Fig. 8.—Kollmann's Urethral Dilator, Type Used for Dilating the Anterior Urethra. (Kny-Scheerer.)

is discontinued and the treatment completed with dilatation and irrigations.

Special urethral dilators of the Oberlaender and Kollmann type give better results than the metal sounds, because in many cases of long-standing inflammation, it is necessary to dilate the urethra as high as 35 or 38 French. When dilators are employed, the blades should always be covered with a rubber sheath.

The foregoing treatment usually clears up a case, in from 6 to 12 weeks; occasionally, we meet with cases that clear up to a certain point and then remain stationary despite all efforts. If these are urethroscoped, one occasionally sees scattered here and there throughout the urethra, large gaping glandular openings surrounded by plaques of scar tissue frequently containing purulent plugs. It is our custom to introduce a fulgurating wire through the urethroscope and destroy the gland with the **Oudin spark.** This procedure should only be performed after the urethra has received a thorough course of dilatation and irrigation.

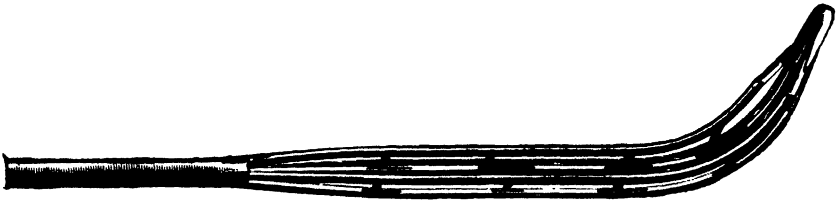


FIG. 9.—KOLLMANN'S URETHRAL DILATOR, ANTEROPOSTERIOR DILATING BLADES. (Kny-Scheerer.)

URETHRAL FISTULA.—Occasionally a persistent fistula, resulting from periurethral abscess, harbors gonococci, which from time to time cause acute relapses of urethral inflammation.

When permanent fistula results, it should be *treated* by **Chetwood's method.** A few drops of a 25 per cent. **ethereal solution of hydrogen peroxid** are injected, preferably through the urethral end of the fistula, employing a hypodermic needle with a blunt point.

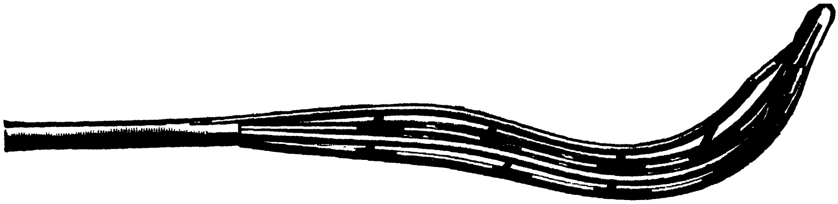


FIG. 10.—KOLLMANN'S URETHRAL DILATOR, BLADES FOR DILATING POSTERIOR URETHRA OR PROSTATE. (Kny-Scheerer.)

If this is not successful, **fulguration** will sometimes obliterate the lumen. The wire is inserted as deeply as possible in the tract, either from the urethral side or, if that be impossible, in the outer opening, and the current turned on until bubbles of gas are seen escaping. In a week this can usually be repeated.

If these methods are not effectual, a **plastic operation** must be done.

STRICTURE.—Urethral stricture resulting from chronic gonorrhea has been variously described as linear, annular, tortuous, irregular, etc.

For prognostic consideration the following points are important:

(i) *Location of the Stricture.*—Strictures located anterior to the penoscrotal junction are less serious and easier to treat than those situated in the bulbous urethra.

(ii) *Caliber of Stricture.*—Infiltrations larger than 25 Fr. are readily dilated and rarely relapse or contract. Infiltrations smaller than 25 Fr. show a tendency to contract after treatment.

(iii) *Is the Stricture Soft or Hard?*—Soft infiltrations are of more recent origin and are readily dilated and rarely relapse. Hard infiltrations mean fixed connective tissue formations, which are difficult and frequently impossible to dilate. They frequently relapse after prolonged dilatation.

(iv) *Is the Stricture Passable or Impassable?*—A patient may have a fair urinary stream in spite of the fact that it is impossible to pass a dilating instrument through the urethra, owing to its irregular and tortuous course. These impassable strictures show a progressive tendency to contract and usually require operative measures for their relief.

(1) *Treatment of Stricture of Large Caliber.*—Infiltrations larger than 15 Fr. come under this heading.

In the passage of **dilating instruments** it should be borne in mind that the brutal passage of a sound, by bruising and tearing the inflamed urethra, sets up a sharp reaction which frequently causes further contraction of the infiltrate by increasing the inflammatory exudate.

The instrument properly sterilized and warmed is introduced into the urethra with the utmost care and gentleness. Its size should correspond to that of the bougie which has been passed through the stricture. When the sound has entered the bladder it is gently withdrawn at once. A second and a third sound may be passed if the first sound has entered easily.

After the passage of sounds, the urethra and bladder are **irrigated** through a soft rubber catheter with 1-8000 **silver nitrate solution.** In addition, the patient is given **hexamethylenamin,** grains x (0.6 gram) before and immediately after instrumentation.

If the treatment is not properly performed, epididymitis, urinary fever, and traumatism to the stricture may result. These complications not only aggravate the patient's condition, but defeat the object of the treatment. They can usually be avoided by the administration of **urotropin** before and after instrumentation, gentleness in the passage of sounds and irrigation of the bladder and urethra immediately following.

The interval between the passage of sounds will depend entirely upon the reaction following. Usually, even after the most gentle instrumentation, a local reaction of more or less intensity appears within 24 hours. The succeeding dilatation should never be performed until the local reaction resulting from the previous treatment has completely subsided. Three days is nearly always a safe interval.

At each subsequent visit, the dilatation is begun with a sound one or two numbers smaller than the last size introduced at the previous visit. The dilatation is then carried on as far as possible without the employment of force.

The "End Point" of Dilatation.—Urologists differ on this point.

Some use the size of the urethral meatus as a gauge, providing it is not congenitally small or contracted by disease. Others disregard the meatus and dilate up to 31 or 32 French.

The following course is recommended: Unless the penis is very small, the urethra is dilated until it will readily admit a 30 French sound. If the meatus is below 25 French, it is cut to 31 French. If larger than 25 French, sounds are passed until the size of the meatus is reached, after which the dilatation is completed with either **Oberlaender** or **Kollmann dilators.**

Irritable and Bleeding Stricture.—Occasionally, even when the utmost gentleness is employed in passing sounds, profuse bleeding follows. When this occurs, dilatation should be postponed, until the congestion has been diminished by a course of irrigations with silver nitrate solutions. In these cases, the use of the Oberlaender dilator instead of sounds is less apt to provoke hemorrhage.

(2) *Stricture of Small Caliber.*—In this class belong strictures of less than 15 French caliber. The dilatation of these tight strictures is best begun with **woven silk bougies,** owing to the danger of making false passages when small metallic instruments are used. When the dilatation with small instruments has been carried up to 15 French, metallic instruments may then be employed.

(3) *Impassable Stricture.*—The urethral infiltrate may be so irregular, nodular and tortuous that neither an olivary bougie or sound can be passed through it. Two types are met with: (1) *uncomplicated impassable stricture,* in which the patient can empty his bladder, although the urinary stream is small; (2) *impassable stricture with retention.* If the patient can void, every effort should be made to pass an instrument into the bladder. Perseverance, gentleness and skill very often succeed.

Technic.—A 4 per cent. **novocain solution** with **adrenalin** (gtts. x: 1 ounce) is injected in the urethra and retained for five minutes. A **filiform** is then introduced into the urethra. If it is caught, others are passed alongside, until the urethra is filled, after which, attempts are made to engage the stricture by manipulating one filiform after the other. If successful in passing a filiform into the bladder, a **tunneled sound** is threaded over the filiform and inserted into the bladder.

If it is impossible to pass a filiform by this method, a **water dilatation urethroscope** (Fig. 1) is introduced into the urethra down to the stricture and its orifice looked for. A filiform then is passed through the urethroscope and an attempt made to guide it through the stricture by direct observation.

Impassable Stricture Complicated by Retention.—When retention occurs, the patient is placed in a **hot bath** for 15 to 20 minutes and should attempt to empty his bladder while in the bath. If he succeeds, an attempt at dilatation should be made, as described in the foregoing section.

If unsuccessful, the bladder should be **aspirated** every eight hours for one day **by suprapubic puncture.** If still unable to void, and another attempt to introduce filiforms is unsuccessful, the stricture is considered impassable.

Indications for Operation.—The types of strictures requiring operation are as follows:

(1) Any stricture that resists dilatation or shows a tendency toward progressive contraction after a course of dilatation.

(2) Impassable stricture, with or without retention.

(3) Resilient stricture.

(4) Tortuous nodular strictures of long standing, and irritable strictures complicated by severe cystitis are best treated by resection or division, especially when located behind the penoscrotal junction.

Type of Operation.—In general, **internal urethrotomy** is performed for strictures located anterior to the penoscrotal junction. If the stricture is of long standing and of small caliber, and complicated by severe cystitis, perineal section is performed, in addition, for drainage.

External urethrotomy is performed for strictures located behind the penoscrotal junction.

When strictures are present in both the pendulous and deep urethra, the **combined operation** is performed.

(2) **Chronic Posterior Gonococcal Infection.**—When gonococcal inflammation invades the deep urethra, there is always some involvement of the prostate. This involvement may be mild or severe. The same holds true for the seminal vesicles; they rarely escape infection when the prostate is affected, owing to their close anatomical relationship.

As a result of chronic inflammation certain changes take place in these structures. The infection first invades the ducts of the prostatic glands and later the glands themselves. At the same time, an inflammatory exudate is deposited in the parenchyma of the glands and also between them in the interstitial tissues. This infiltration causes the mucous membrane of the acini to become swollen. The lumen of the gland ducts becomes narrowed, so that the drainage of inflammatory products produced within the glands themselves is interfered with.

The inflammation frequently extends through the ejaculatory ducts and involves the seminal vesicles. The mucous membrane of the ducts becomes swollen and the lumen narrowed, causing retention of products and suppuration within the vesicles.

The same changes take place in the urethra and verumontanum, so that if the condition is not relieved, the round-cell infiltration becomes organized and sclerosis results. This sclerosis causes either partial or complete obstruction of many of the prostatic glands, resulting finally in obliteration of the ducts with focal suppuration and destruction of the prostatic parenchyma.

As a result of these changes, the deep urethra becomes hypersensitive, the secretions of the prostate and vesicles become altered and symptoms of irritable or atonic impotence, sexual neurasthenia and sterility are added to the clinical picture.

The indications for *treatment* are (1) to cause absorption of the inflammatory exudate, thereby restoring glandular drainage and function; (2) to destroy the gonococcus.

To accomplish this, the following measures are employed:

(1) Massage of the prostate and vesicles.
(2) Dilatation.
(3) Irrigations and instillations.
(4) Heat.
(5) Urethroscopic treatment.
(6) Operative treatment.

MASSAGE.—The object of **massage** is to expel the purulent material plugging the ducts of the prostatic glands and also to express the accumulated secretions in them.

Technic.—A rubber cot is placed over the index finger. A 2-inch bandage is wrapped around the knuckles to protect them from being soiled. The finger cot is then lubricated with vaselin and gently inserted through the anal sphincter into the rectum.

The prostate is then gently but thoroughly massaged by a side-to-side motion, beginning at the upper borders of the gland and gradually reaching the apex. This manipulation is continued for several minutes if well tolerated.

The vesicles are next treated similarly. The finger reaches up as far as possible and presses upon the vesicle, gradually withdrawing the finger with a to-and-fro lateral motion until the prostate is reached. Special attention should be given to the junction of the vesicles and prostate, because at this point there is usually a deposit of periprostatic exudate. The massage of the vesicles is kept up until there is a distinct reduction in size. Any secretion expelled through the urethra is placed on a slide and examined for pus and gonococci. If well borne, massage can be given three times a week, and is kept up until all pus disappears.

Contra-indications.—Massage should be kept up if it relieves the subjective symptoms. If it increases them, then it is harmful. Massage is dangerous in acute inflammation of the urethra, prostate, vesicles and epididymis. If bleeding follows, the manipulation has either been too severe or there is an acute process, either in the vesicles or in some part of the prostate. When this occurs, massage should be discontinued until bleeding has completely stopped.

DILATATION.—**Dilatation** of the prostatic urethra helps to promote absorption of urethral and periurethral infiltrations.

The instrument most suitable for dilating is the posterior Kollmann dilator. With this instrument, the urethra can be dilated up to 45 or 50 French. Some urologists prefer the irrigating type of the Kollmann dilator. The authors do not employ them. They rust at the joints and get out of order very easily; furthermore, they are hard to keep clean.

Technic.—The instrument should always be covered with a rubber sheath. It is lubricated by dipping into sterile glycerin and gently inserted into the deep urethra. The dilating screw on the handle-end is then turned until the patient complains of pain. At the next treatment, the dilatation is carried one number higher. Usually dilatation up to 40 Fr. is sufficient for most cases. Dilatation is usually tolerated twice a week. Dilatation may be well borne three times a week.

Contra-indications.—When the urine contains free pus or the gonococci persist, dilatation is dangerous. When the urine is only slightly cloudy and contains many shreds, dilatation is most serviceable and practically free from danger. Still one should always remember that if it is too rapidly or too frequently performed, acute prostatitis or epididymitis may result. If excessive bleeding follows, it should not be repeated until the patient has received a course of massage and irrigations.

IRRIGATIONS.—The drug of choice is **silver nitrate,** beginning with 1-8000 and gradually increasing in strength, administered according to the methods previously described.

INSTILLATIONS.—In the terminal stages of chronic posterior urethritis, when shreds and pus still persist in the morning urine, urethroscopic examinations may reveal erosions and granulations in the lateral prostatic sinuses. These usually respond to instillations of **nitrate of silver,** beginning with ½ per cent. and gradually increasing to 3 per cent. If they still persist, stronger solutions applied through the urethroscope are necessary to destroy them.

URETHROSCOPIC TREATMENT.—This form of treatment is occasionally indicated in the terminal stages of chronic posterior urethritis, when granulations, erosions, papillomata and polypoid excrescences are present in the urethra.

The drug employed is **silver nitrate** in strengths ranging from 5 to 20 per cent. The stronger solutions should be carefully applied with cotton mopped around fine applicators, at intervals of 5 to 10 days, the interval depending on the intensity of the reaction.

The Young straight urethroscopic tube is recommended in preference to the beaked posterior urethroscopes of the Swinbourne type.

The previous instillation of 4 per cent. **novocain, aposthesin** or **alypin** lessens the pain of the manipulation.

Urethroscopic applications are sometimes useful when the verumontanum remains large and edematous, giving rise to urethral irritability and neurasthenia.

HEAT.—**Heat** is applied to the prostate and vesicles through the rectum, either by means of the **bipolar high frequency current** or the **hot rectal douche.**

Hot rectal douches may be given either with a closed metal tube, the psychrophore, or through a double current tube, of the Chetwood, Guiteras or Tuttle type. The patient fills a two-quart douche bag with water and suspends it about three feet above the toilet seat. He then seats himself and inserts the lubricated tube into the rectum for about four inches and turns on the water. The temperature of the water is usually 120° F. (48.9° C.), or as hot as the finger can bear. The douche should be repeated daily and stopped when the bowel becomes irritated.

Heat may be applied to the prostate by the **D'Arsonval current.** The patient is placed on the table and a thick metal electrode is placed in the rectum. Another large flat electrode is placed over the suprapubic region. From 800 to 1500 milliamperes may be borne comfortably for 15 to 20 minutes.

Operative Treatment.—In the absence of stricture or abscess, operative procedures are rarely called for in cases of chronic gonorrhea. In order to cure persistent infection of the seminal vesicles, Belfield advocates exposing the vas through an incision in the scrotum. He then incises the vas and injects into the proximal end, either **10 per cent. argyrol** or **4 per cent. collargol** and fixes the duct in the wound so that any discharge will escape through the wound itself and not into the scrotum. The object of the operation is to secure antisepsis and drainage of the vesicles. Excellent results are claimed by him from this operation. Fuller recommends **vesiculotomy** through a perineal incision. There is no doubt that his operation unquestionably relieves the rheumatic pains in a great many cases; on the other hand, it frequently fails. Cabot recommends **vesiculectomy,** claiming that it is impossible to drain a tortuous tube like the vesicle by simple incision. The objection to his operation is that it is very frequently followed by impotence.

Experience has shown that these operative procedures should be employed only in intractable cases after every other method has been thoroughly tried out.

Routine Treatment of Chronic Posterior Gonorrhea.—The type of treatment will depend upon whether the second urine is clear, with shreds, or slightly cloudy (due to small amounts of free pus).

In the former instance, when the urine is clear but contains many shreds, the treatment is begun with **silver nitrate irrigations** given through a catheter (*see* page 483), beginning with 1 : 8000. These irrigations are given every other day. Usually after a week massage may be begun.

The patient reports with a full bladder. He voids the first half of the urine in two glasses. The prostate and vesicles are then gently but thoroughly massaged, after which the patient voids the remainder of the urine. The urines are examined. The treatment is completed by an irrigation of nitrate of silver. Some urologists inject **argyrol** into the bladder or distend it with the silver solution, claiming that it is easier to massage the vesicles and prostate when the bladder is full and also that epididymitis is prevented in this way. The authors find this preliminary antisepsis unnecessary and cumbersome. Furthermore, it is much more trying to the patient to be massaged when the bladder is filled with silver solution.

When the urine clears up and it is seen that local treatment is well tolerated, **dilatation** may be begun. The routine is as follows:

Having massaged the prostate and vesicles, as previously described, the patient is placed on the table. The Kollmann dilator, properly lubricated, is introduced and dilatation performed until pain is complained of. The dilator is then gently withdrawn, after which an irrigation of silver nitrate is given.

The intervals between treatments will depend entirely upon the temper of the urethra. Some patients tolerate treatment three times a week, others less often. If dilatation causes most irritation, it should be given less often than massage and irrigations. In all cases, the treatment is not repeated until all reaction from the previous one has ceased.

If symptoms of over-treatment occur, as shown by increasing cloudiness of urine and irritability of the urethra (frequency and precipitancy of urination), all local treatment is stopped until they have subsided.

When the second urine contains much free pus, it is safer to begin the treatment with the **organic silver salts,** preferably **argyrol** 20 per cent. freshly prepared. **Instillations** are given every day. When the urine becomes almost clear, and it is determined that local treatment is tolerated, then the local treatment previously described is cautiously begun.

(3) **Chronic Anteroposterior Gonorrhea.**—When the infection involves the anterior as well as the posterior urethra, it is impossible to outline a routine method which will apply to all cases, because it is sometimes difficult to decide, in the beginning, which of the various lesions along the urethra or in the prostate is the important one requiring immediate attention. It is important, however, to bear in mind that whatever form of local treatment is given it should be for the definite purpose of curing a known lesion. The effect of treatment should be closely watched. Unless improvement is noted, the treatment must be changed. To the beginner, the management of these cases is at times perplexing and disappointing.

The various therapeutic procedures have already been described in detail; their proper application will depend entirely upon the experience and judgment of the physician.

(4) **Acute Exacerbations of Chronic Gonorrhea.**—The management of these cases will depend entirely upon the symptomatology, physical signs and urinary findings. At times, they simulate acute anterior urethritis, others appear as acute posterior infections, while a third variety shows symptoms of both acute anterior and posterior involvement.

Complications of Gonorrheal Urethritis and Their Treatment

Genito-urinary Complications.—Folliculitis.—As a result of suppurations of one or more urethral follicles, retention of pus may occur, forming small abscesses. These usually escape notice during the acute stage of the disease. When they occur during the declining stage, they cause a characteristic return of symptoms. After a day or two of indefinite localized itching or uneasiness, the discharge, which previously was very scant and mucoid in character, becomes profuse and purulent. The meatus may even become inflamed. The characteristic feature of the discharge is that it lasts but a short time, and stops as suddenly as it began.

Treatment.—During the acute stage no special treatment is required.

The usual local treatment of urethritis, if persisted in, will nearly always clear up the abscesses. The treatment of acute relapses of chronic folliculitis will be considered under chronic urethritis.

PERIURETHRAL ABSCESS.—The suppurative process from an infected urethral gland may extend to the periurethral connective tissue. These abscesses usually appear alongside the frenum, in the pendulous portion, or in the perineum, in which case Cowper's glands may be involved. Abscesses forming beside the frenum grow rapidly. They either open spontaneously or require **incision.** In either case, they may close spontaneously or require special treatment for their cure. When the resulting fistula shows no tendency to close it should be injected with a **25 per cent. ethereal solution of hydrogen peroxid,** preferably through the urethral end. This may be repeated every three days until the fistula closes. If it does not yield to this treatment, a **plastic operation** is necessary.

Periurethral abscess of the pendulous portion usually develops quite slowly. It either resolves or ruptures into the urethra. More frequently, it invades the skin and points directly opposite the point of origin. More rarely, the pus may travel beneath the fascia for a considerable distance before rupturing externally, unless promptly excised. The fistulas, unless large, heal spontaneously. The *treatment* consists in laying the abscess cavity **open freely** as soon as fluctuation is noticed, evacuating the pus and allowing it to heal by granulation.

In abscess formation in Cowper's glands, the abscess usually appears on one side of the median line. The pus may travel some distance beneath the deep fascia before breaking through, causing extensive perineal infiltration, and frequently multiple persistent fistulas. The treatment is **wide and free excision.**

SPONGEITIS AND CAVERNITIS.—Inflammation of the erectile tissues is an extremely rare complication of gonorrhea. The treatment consists of **rest in bed, hot or cold applications,** and **incision** if abscess occurs.

INGUINAL ADENITIS, LYMPHANGITIS.—These complications are due to the extension of the gonorrhea beyond the urethra. The adenitis consists of an inflammatory enlargement of the glands in the groin, which rarely suppurate.

Special *treatment* is rarely necessary. If marked, or if pain is present, the patient is **put to bed** and **heat** or **cold** applied. Painting the skin over the gland with **iodin** and applying a **glycerin compress** seems to hasten resolution and relieve pain in severe cases. If suppuration occurs it should be treated as bubo.

BALANITIS.—This consists of an inflammation of the mucous membrane of the prepuce and glans penis. It occurs in men with long foreskins and in persons of uncleanly habits.

The *treatment* consists in **bathing** the parts with soap and water. If much inflammation and discharge are present, a small pledget of cotton is soaked in **lotio nigra.** This is placed around the glans and the foreskin is drawn over it. Later the following **dusting powder** is used:

℞
Bismuthi subnitratis
Calomel āā ʒii (8.0 grams)
Acidi borici
M. Ft. Pulv.
Sig.: Apply externally.

Sometimes the swelling of the foreskin is so great that it cannot be retracted. This condition is called *phimosis.* The treatment consists in **prolonged soaking** of the penis **in hot water.** The patient should also be instructed to inject **protargol** 1/4 per cent. under the foreskin. If the swelling and edema persist or if gangrene threatens, an **incision** is made through the prepuce on its dorsal aspect. This can be done painlessly under local anesthesia. Sometimes a long and tight prepuce is caught behind the glans and cannot be drawn over it. This is called *paraphimosis.* The treatment consists in drawing the foreskin over the glans by **manipulation.** In severe cases, preliminary prolonged soaking in hot water facilitates the reduction. If it is impossible to accomplish this, the constricting band should be incised on the dorsum, which generally permits prompt reduction.

Acute Prostatitis and Prostatic Abscess.—Acute gonorrheal inflammation of the prostate occurs in all degrees of severity. The prostatitis may be so mild as to add scarcely any symptoms to those of urethritis. When there is marked involvement, definite constitutional and local symptoms are present. Since acute prostatitis cannot be differentiated from prostatic abscess they will be considered together.

Increase in Local Symptoms of Posterior Urethritis.—In addition, the patient complains of a dull aching or throbbing pain, which is felt either in the rectum, hypogastrium or in the pelvis, radiating down to the testicles and thighs.

Dysuria.—In addition to frequency and urgency of urination, the urinary stream is smaller and weaker. It may be intermittent. In marked enlargements, complete retention may occur. Defecation may be painful and difficult.

Chills and Fever.—Very often a severe chill ushers in the febrile period. The degree of fever is no index, however, to the degree of the prostatic involvement. Quite frequently, there is an absence of fever in severe cases.

Local Signs.—One or both lobes of the prostate are always enlarged. When the whole gland is involved, it may become so large that it is impossible to reach its upper border with the examining finger. The gland feels hot, hard and is tender to the touch.

Resolution may occur or the inflammation may become chronic. The abscess may rupture into the urethra, rectum or into the periprostatic tissue, causing ischiorectal abscess.

Most prostatic abscesses, fortunately, rupture into the deep urethra. Sometimes they point into the rectum or perineum. In rare instances, the pus, burrowing forward into the perineum, extends along the corpus cavernosum, causing considerable infiltration and slough. It has been known to follow the various fascial planes and point in the inguinal canal and even in the space of Retzius, in neglected cases.

Treatment.—As soon as the complication is recognized, all urethral treatment is stopped. In mild cases the treatment is that of acute posterior urethritis. **Hot rectal douches** are ordered twice a day. **Vaccines** are indicated. Their prompt administration may sometimes prevent or abort abscess formation.

In severe cases, where there is much urinary distress and fever, the patient is **put to bed** and a **hot-water bag** applied to the perineum. Hot rectal douches are given every four hours. To relieve the urgency and tenesmus attending urination, the following **rectal suppository** will be found useful:

℞
Morphinæ sulphatis ....grain ¼ (0.016 gram)
Quininæ sulphatis ....grains x (0.65 gram)
Olei theobromatis........... q.s.
M. Ft. Rectal suppositories.

Sig.: Insert 2 to 3 times a day.

If there is acute retention, the bladder is emptied with a soft rubber catheter, size 12 to 14 French, every six hours, after which ½ ounce (15 c.c.) of **10 per cent. argyrol** is instilled into the bladder and deep urethra. If, in spite of this treatment, acute retention is not relieved in a few days, or if the temperature remains high and there is prostration, **surgical interference** is indicated. Opening the abscess through the perineal route gives prompt relief, thereby preventing the miserable and even fatal results following prolonged palliative treatment.

Seminal Vesiculitis.—Acute seminal vesiculitis always occurs in conjunction with acute posterior urethritis and prostatitis. It usually adds nothing to the symptomatology, except that in rare instances, when there is a marked unilateral involvement, the patient may complain of pain in the groin or in the lumbar region on the corresponding side. Occasionally, a rather profuse terminal hematuria ushers in a vesiculitis.

By rectum, the vesicles feel thickened, hot and very tender. If there is pus retention, a tense sausage-like tumor is felt above the prostate on one or both sides. The abscess usually terminates by resolution, but may rupture into the rectum, peritoneum or ischiorectal fossa.

Treatment.—The treatment of acute seminal vesiculitis is the palliative treatment of acute prostatitis. If an abscess forms and shows a tendency to spread, **vesiculotomy** is indicated.

Epididymitis.—Inflammation of the epididymis is caused by the passage of gonococci from the posterior urethra through the vas deferens, or by extension of the inflammation along the lymphatics of these canals.

The inflammation is usually limited to the epididymis, although the testicle is often apparently enlarged, because it is surrounded by the inflamed epididymis. Frequently, there is an effusion of serum in the sac of the tunica vaginalis, causing the testicle to appear larger than normal.

Etiology.—The direct causative factor is invasion by the gonococcus. Some patients are more prone to epididymitis than others, because, in spite of every precaution, this complication will occur; while others, disregardng all hygienic precautions, go about with an acute gonorrhea, indulge in sexual excesses and alcohol and yet escape. Abortive and strenuous local treatment are, very frequently, exciting factors.

If the modern moderate local treatment is properly administered and if the patient wears a well-fitting suspensory bandage and abstains from violent exercise—horse-back riding, dancing, sexual excitement and the use of alcohol—in most instances he will escape this complication.

Pathology.—The inflammation begins in the globus minor. If mild, the infection is confined to this end of the epididymis. If severe, it may extend throughout the organ, causing infiltration, hardening and enlargement with the formation of focal abscesses. The tunica may become acutely inflamed and hydrocele result, but the testicle rarely takes part in the inflammation. The vas deferens may be slightly thickened and tender.

Symptoms.—An indefinite dragging sensation is first felt in the testicle, radiating upward into the groin. Pain and swelling of the epididymis comes on rapidly. Within a few hours, the epididymis is large, hot and exquisitely tender. The scrotal tissues may become red, thickened and edematous. The inflamed mass may reach the size of a fist. Standing, walking, bending or lifting aggravates the pain.

The urethral discharge usually disappears or diminishes noticeably with the onset of the epididymitis, only to reappear again when the inflammation subsides.

Examination shows the epididymis enlarged, hard and tender. The testicles cannot be outlined. The spermatic cord is thickened and tender.

Prognosis.—As the inflammation advances, the pain and swelling increase in intensity. Within a few days the symptoms gradually subside. Resolution begins rapidly, but progresses more and more slowly, until it seems to remain stationary. The globus minor is the last to clear up. The little hard lump in the epididymis known sometimes as the "gonorrheal nodule" may be permanent. It causes no uneasiness and is not sensitive to pressure.

There is no danger to life, sexual desire or potency. Sterility of the affected side is not uncommon. Relapses may occur. If both sides have been affected, sterility may be caused by the formation of a permanent inflammatory infiltrate, plugging up or compressing the efferent duct of the epididymis. Atrophy of the testicle never occurs, unless there has been an accompanying orchitis.

Treatment.—Much can be done to avoid this complication by using the utmost care and gentleness in the treatment of posterior urethritis. Vigorous local treatment when begun too soon, or rough instrumentation, may be exciting factors.

The patient should be instructed to wear a proper-fitting suspensory

Practice of Medicine—Tice.

☛ Insert following page 504, Vol. III. (Do not take out any old page.)

SCROTAL SUPPORT.

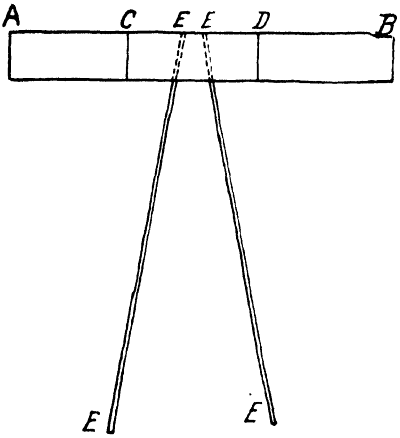


FIG. 5a

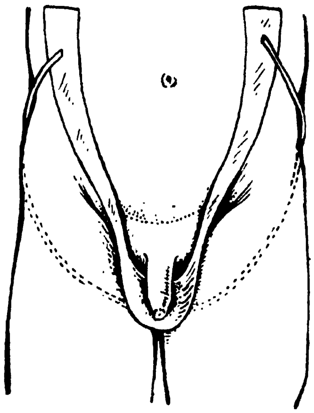


FIG. 5b

This support devised in Bellevue Hospital and made of adhesive will be found far superior to any jock strap or suspensory on the market. When properly applied the patient can attend to his work in comparative comfort.

It consists of a strip of adhesive plaster thirty inches long and three inches wide A–B. At a point near the midline are attached two strips of plaster one half inch wide and twenty inches long E–E. To prevent the plaster from adhering to the scrotum, a shorter strip eight inches long and three inches wide C–D is applied to the middle portion of A–B. The strip A–B acts as a sling for the scrotal contents, as shown in Fig. 5 b, the exposed adhesive side being applied to the sides of the abdomen. The patient lies on his back while the surgeon holding the scrotum well up towards the abdomen with one hand adjusts the support as in Fig. 5 b, after which the strips E–E are drawn backward between the thighs and well around them. These serve to hold the sling in position, preventing it from slipping forward. The support is reinforced by additional strips similar to A–B, and several more transversely placed above the symphysis. Before applying the plaster the scrotum is covered with absorbent cotton or gauze.

only, which do not yield to treatment, and for persistently recurring cases.

Renal Infection.—Renal infection due to gonorrhea is rare. Pyelonephritis may occur in very severe cases. Usually it is mild in its course. The treatment is similar to that for pyelonephritis due to other bacteria.

Bones and Joints.—Gonorrheal Rheumatism.—The term, "gonorrheal rheumatism," includes all metastatic gonococcal inflammations involving the synovial membranes of joints, tendon sheaths, bursæ, etc.

Occurrence.—Different observers have estimated that rheumatism occurs in from 2 to 8 per cent. of cases of gonococcal infection. It is difficult to arrive at anything approaching an accurate conclusion, especially in those cases where there is an apparent absence of local genital or urethral infection, because so many cases of gonococcal rheumatism are not diagnosed, as such, owing to lack of knowledge or to suppression of a previous history of gonorrhea.

Males are more liable than females. In young girls and children, the tendency to rheumatism is more pronounced than in adult females; it may follow vulvovaginitis or ophthalmia neonatorum.

One or several joints may be affected. In order of relative frequency, the joints involved are the knee, ankle, wrist, fingers and great toes, elbow, shoulder, hip and jaw. Tenosynovitis and periarticular involvement should excite suspicion as to the nature of the inflammation.

Pathology.—The gonococcus reaches the synovial membranes by the blood stream. Round-cell infiltration of the tissues, edema and serofibrinous effusion follow. Later, adhesions are produced which limit the movements of the parts. The inflammation may go on to pus formation. Secondary infection by staphylococci or streptococci may supervene, in which case, erosions of the cartilage and destruction of the joint may be expected.

Clinical Forms.—Clinically, the following types are met with:

(1) *Arthritic,* in which one or several joints may become involved.

(2) *Hydrarthrosis,* usually monarticular, particularly liable to involve the knee.

(3) *Bursal or synovial form,* in which the tendons and their sheaths, bursæ (e.g., of the patella, the olecranon or the tendo achillis) and periosteum are involved. The articulations may not be affected.

(4) *Arthralgic,* in which there are wandering joint pains with or without redness and swelling.

Keyes employs the following classification:

(i) *Gonorrheal arthritis,* in which the organisms are located in the joint itself, and

(ii) *Gonorrheal osteo-arthritis,* in which the gonococci are localized in the articular extremities of the bones, and any effusion into the joints is secondary.

Symptoms.—In the acute type the onset is sudden, the temperature rising to 103° F. (39.4° C.). The inflammation begins like an attack of acute articular rheumatism, with redness, swelling, extreme tenderness and loss of function. There is usually some effusion into and around the joints. In severe cases, the tendon sheaths and bursæ become involved, with increase of the effusion in the joint and also periarticular edema. The onset may be subacute, with local pain and tenderness and moderate to severe disability. The duration of the attack is usually long. The mildest lesion may persist for months.

Diagnosis.—When acute rheumatism occurs during the course of gonorrhea, the diagnosis is not difficult. Marked swelling of a joint, with periarticular involvement, giving a fusiform appearance to the joint, and a positive complement-fixation test fix the diagnosis.

Chronic gonorrheal arthritis is differentiated from other forms of arthritis by means of the complement-fixation test.

When acute rheumatism occurs, in cases with no history of gonorrhea or apparently no urethral or genital lesion, in which there is no perspiration and no response to the salicylates, the serum reaction will prove of service in making a diagnosis.

Sometimes the gonococcus can be identified in the fluid aspirated from the joint. Frequently, the fluid does not yield the organism. In addition, a careful routine examination should be made of the urinary and genital tracts.

Treatment.—Proper local and internal treatment of the urethritis is the best prophylactic. If fever appears during the course of a gonorrhea, the administration of **vaccines** may possibly have a prophylactic action.

With the onset of the attack, the patient is **put to bed.** For the relief of pain, the **joint** is **immobilized** with a light splint, preferably of plaster-of-Paris. The **Bier treatment,** or exposure of the joint to **hot air,** should be employed. If the pain is severe, applications of equal parts of **ichthyol** and **glycerin** may afford relief. When the pain is very severe, stroking the joint lightly with the **actual cautery** frequently gives immediate relief.

The use of **vaccines** in some cases often gives definite and satisfactory results; in others, the results are entirely negative.

The tendency to the formation of adhesions must be kept in mind and gentle **passive motion** employed to prevent ankylosis, remembering, however, that too early or too forcible passive movements may light up a subsiding inflammation.

The usual **antirheumatic remedies** are usually quite useless.

The **diet** should be ample and similar to that in chronic gonorrhea. Restrictions are not necessary.

Systematic gentle **massage,** in the subsiding stages of the inflammation, helps to diminish the muscular atrophy occurring in the prolonged chronic cases.

If the effusion into the joint is not arrested by immobilization and baking, the **fluid should be aspirated** under the most careful asepsis. In most cases this is unnecessary. Fuller advises **seminal vesiculotomy** in these cases on the ground that the local focus, which causes systemic infection, is present in the seminal vesicles. The precise status of this operation, in the treatment of gonorrheal rheumatism, is not yet definitely established. In some cases it succeeds, in others it fails.

The prostate and vesicles should be gently and thoroughly massaged every day unless they are acutely inflamed. Resulting deformities and loss of function are treated by **orthopedic methods.**

EXOSTOSIS OF THE OS CALCIS.—The inflammation begins as a periostitis or myositis at the attachment of the flexor brevis digitorum to the tubercle of the os calcis. When the acute inflammation subsides, an exostosis forms. Pressure upon this while walking causes great pain. The diagnosis is made by radiography. The treatment is chiseling away of the exostosis through an incision along the inner side of the heel.

Gonococcal Affections of the Heart and Blood-vessels.—ENDOCARDITIS.—Ricord in 1847, and Brandes in 1854, were among the first to recognize that endocarditis could be caused by gonococci circulating in the blood of susceptible patients suffering from gonorrhea. In 1895, Thayer and Blumer cultivated the gonococcus from the blood of a patient suffering from acute endocarditis.

Pathology.—No characteristic feature has been described which would differentiate the gonococcal from other forms of endocardial inflammations. Vegetations composed of fibrin and infiltrated with leukocytes and gonococci, erosions, ulcerations and valvular destruction are found. The *diagnosis* is dependent on the isolation of the gonococcus. A few cases, in which streptococci and staphylococci were found in conjunction with gonococci, have been reported.

Symptoms.—In most cases, the symptoms are less acute than in ulcerative endocarditis due to other organisms. Temperature ranges from 101°-103° F. (38.3°-39.4° F.). Dyspnea, precordial distress and palpitations are present. Sooner or later, the usual auscultatory signs appear. The lesions are usually confined to the left side of the heart. The relative frequency in which the various valves are involved is as follows:

Mitral, 48 per cent.
Aortic, 39 per cent.
Pulmonary, 5.3 per cent.
Tricuspid, 2.6 per cent.

Embolic metastasis may involve the spleen, liver, kidneys, etc. Men are more frequently attacked than women, and women are more susceptible during pregnancy and the puerperium.

Treatment.—The treatment will be described under septicemia.

PERICARDITIS.—This occurs very infrequently. The amount of effusion is seldom great. In rare cases, aspiration was required to relieve the dyspnea. The fluid may be serous, serofibrinous or purulent.

PHLEBITIS.—The prostatic plexus of veins and the pampiniform plexus of the spermatic cord and of the broad ligament are the most common areas to be primarily affected.

Treatment.—In addition to the care of the genital focus and of the septicemia, **complete rest** of the affected parts should be secured.

GONOCOCCAL SEPTICEMIA.—The first to separate the gonococcus from the blood stream was Hewes, who, in 1894, isolated the organism from the blood obtained from a case of gonorrheal arthritis.

Lofaro believes that the gonococcus reaches the blood through the lymphatics, but in some cases direct entry into a blood-vessel, associated perhaps with venous thrombosis, is the origin of the systemic infection. Owing to a deficiency in the resistance of the individual, septicemia results, which may either run a short acute course ending in recovery or death, or it may become chronic, with a liability to acute exacerbations.

Predisposing Factors.—Among these are traumatism, caused by unskillful instrumentation, alcoholic and sexual excess, menstruation, pregnancy and any general condition lowering the power of resistance, such as tuberculosis and diabetes.

Symptoms.—In acute cases the symptoms are similar to those of sepsis caused by any pathogenic microörganism. The temperature may resemble typhoid fever or pyemia. The spleen is frequently enlarged, and the liver may be felt below the costal margin or it may be atrophied with symptoms of jaundice. Albuminuria and cutaneous eruptions or petechia may be present.

In very severe cases, there is headache, thirst, profuse perspiration, vomiting, diarrhea and death.

In chronic cases, the symptoms are much less severe and sometimes the condition is mistaken for toxemia.

Diagnosis.—The diagnosis is wholly dependent upon the isolation of the organism from the patient's blood.

Complications.—Arthritis is the most frequent complication. The most important one is endocarditis. Pericarditis, meningitis, pneumonia, peritonitis, pleurisy, iritis, conjunctivitis, thrombosis and embolism may occur.

Prognosis.—The prognosis will depend upon the intensity of the septicemia and the gravity of the complications. It should always be guarded in acute cases, because of the difficulty in stimulating the formation of antibodies, and in subacute cases because of the danger of serious complications.

Treatment.—The first indication is to **open and drain** any abscess cavity, however small, providing the patient's condition permits it.

The temperature, if high, may be controlled by **alcohol sponging, cold packs or baths.** The **diet** should be sustaining and easily assimilated. **Alcohol** is contra-indicated. **Antigonococcic serum** seems of more value than vaccines in acute cases. An injection of 15 to 25 c.c. every four hours is given.

In chronic cases, **vaccines** are said to be more beneficial. Satisfactory results have been reported with the **intravenous injection of colloidal silver** given in doses of 10 c.c. every three or four days.

Complications arising during the course of the septicemia should be treated along the usual lines.

Gonococcal Infections of the Eye.—The eye may become infected with the gonococcus either through direct inoculation from without or through the blood stream.

Etiology.—The great majority of cases are due to accidental contamination of the conjunctiva either from handkerchiefs, towels, hands or during the passage of the child through the genital tract of the mother infected with gonorrhea.

Infants are especially susceptible to gonorrheal conjunctivitis. Since the conjunctivitis of infants, known as "ophthalmia neonatorum," differs in some respects from the disease as seen in adults, it will be considered separately.

OPHTHALMIA NEONATORUM.—When the infant's eyes are infected in the parturient canal, the infection usually occurs while the eyes are passing over the perineum, as the lids at this moment are most liable to become separated.

Infection may take place in utero, the organisms in this instance penetrating into the amniotic fluid, in which case the child is born with a well-developed ophthalmia. Cases have been reported in which the eyes were completely destroyed at birth.

Inoculation of the eye is very liable to occur during the cleansing immediately after birth. Gonococcal pus from the cervix, adhering to the child's face, may be washed into the eye by the nurse or rubbed into it by the hands of the infant.

Symptoms.—Evidence of the disease is usually present in the first 48 hours. The earliest symptoms are those of irritation, viz., redness of the conjunctiva and excess of serous secretion. The redness increases and spreads and the lids become intensely red and swollen. The secretion rapidly becomes purulent and glues the lids together. On separating the lids, pus freely exudes. In untreated cases, the inflammation goes on to ulceration of the cornea with sloughing, resulting in opacities and defective vision or even total blindness. In many cases the whole eyeball may be completely destroyed.

Diagnosis.—Almost every inflammation of the infantile conjunctiva of increasing severity and associated with the formation of thick profuse pus is gonorrheal. The microscope determines the diagnosis.

Prognosis.—The prognosis depends entirely upon the stage at which the disease comes under treatment. If sloughing ulcers of the cornea are present, there is always some impairment of vision. In children suffering in addition with congenital syphilis the outlook is very grave.

Prophylaxis.—At birth a germicide should be dropped into the eyes of every child. There should be no exception to this rule of practice. Credé recommended 2 per cent. **silver nitrate.** Many observers, notably Stephenson, find that 1 per cent. silver nitrate is equally efficient. Others employ the **organic silver salts.** Darier, of Paris, uses 15 per cent. freshly prepared **argyrol.** Others use protargol 3 to 5 per cent.

Treatment.—**Cold applications** form an important part of the treatment. They must be kept up night and day. Thin pads of gauze, chilled in ice water, are placed over the closed lids. These are renewed every five minutes day and night. If the cold is too intense, the nutrition of the cornea may be interfered with, evidenced by a misty or cloudy appearance beginning at the center. When this occurs, the cold should be stopped at once and not renewed until the cornea clears up.

In addition, a few drops of 20 per cent. freshly prepared **argyrol** are dropped into the inflamed eye every hour. When the inflammation begins to subside and the discharge becomes mucopurulent, a 1 per cent. **silver nitrate** solution is applied once a day, until no gonococci can be found in the secretions.

If only one eye is involved, every precaution should be taken to protect the healthy eye. Various methods have been employed. Knapp employs a **mica spectacle plate,** which can be obtained from any optician. It is transparent, light and does not steam. It is fastened on with adhesive strips.

GONOCOCCAL CONJUNCTIVITIS IN THE ADULT.—The incubation period is about three days. The onset is hyperacute and there is pronounced pus formation. Corneal complications are more frequent and more severe than in infants. Chemosis, rare in the infant, is a feature of the disease in the adult. When pronounced, early and dangerous forms of ulceration may be anticipated.

Treatment.—The treatment is the same as in infants. When the cornea is involved, **atropin** ½ per cent. or **eserin** is employed.

Vaccines and **sera,** in the infant and adult types, are employed by many as a routine measure. In most cases they have not proven successful.

SYSTEMIC OCULAR GONORRHEA.—Byers enumerated the various lesions that may occur as a result of systemic metastatic infections as follows: iritis (Mackenzie), conjunctivitis (Fournier), iridochoroiditis (Koeniger), keratitis (Colsmann), panophthalmitis (Martin), optic neuritis (Panas), retinitis (Burckhardt) and thrombosis of the retinal vessels (Galezowski).

Iritis or iridocyclitis may appear as a feature of systemic gonorrhea. It shows a tendency to recur with each attack or relapse of urethritis. It is usually mild, in which case it is frequently overlooked, or it may be severe and compel attention.

Conjunctivitis is nearly always bilateral.

Symptoms.—The symptoms are much milder than in cases due to direct inoculation. Gonococci are usually found in the discharge. The average duration is two weeks and the prognosis is good.

When the retina is involved, the lesion is a neuroretinitis which may be unilateral or bilateral. In nine cases reported by Byers, six recovered and three terminated in atrophy.

Diagnosis.—Systemic ocular disease is more likely to be mild, bilateral and is always associated with genital gonorrhea and gonorrheal arthritis. The finding of the gonococcus in the ocular disease and a positive fixation test prove the nature of the lesion, but may leave doubt as to whether the eye condition is local or metastatic.

Treatment.—Conjunctivitis is treated as described in the foregoing section. Other local treatment is along general lines; e.g., **atropin** for iritis, etc. The genital gonorrhea should be vigorously treated. **Vaccines** and **sera** may be administered but are of doubtful value.

Buccal and Nasal Gonorrhea.—Ahlfeld and Kimball have reported cases proving the existence of gonorrheal inflammations of the mouth and nose in infants. In the adult the evidence of its existence is very inconclusive.

In infants, the inflammation is confined either to the nose or mouth and is severe in character. In some cases the nasal gonorrhea has accompanied ophthalmia neonatorum.

Treatment.—Buccal gonorrhea readily clears up with the use of antiseptic mouth sprays, e.g., **Dobell's solution, boric acid,** etc.

Nasal gonorrhea is treated with argyrol 20 per cent. dropped into the nose three times a day.

Gonorrhea of the Anus and Rectum.—*Etiology.*—The anus and rectum are relatively quite resistant to gonococcal infection. In 1037 cases of genital gonorrhea collected by Howard, Baer and Schultz, the anus was implicated 157 times. In men, sodomy is accepted as a cause for anal gonorrhea. In women, inoculation occurs from the vulvar discharge or from the douche tube or hands.

Pathology.—The epithelium of the rectum is eroded, infiltrated and ulcerated. Fissures and condylomata are common.

Symptoms.—Usually the symptoms are slight, and frequently overlooked. In the severe cases there is intense itching and burning. Rectal pain and blood-streaked stools are noted when ulcerations are present. Locally, the anal orifice may be swollen or fissured. Condylomata may be present. Pus can sometimes be expressed by pressure from the rectum. Rectal inspection may reveal tumefaction, erosion and ulceration.

Diagnosis.—The diagnosis is confirmed by the microscope, and culture should be done in doubtful cases.

Treatment.—Early cases are treated by injections of ½ ounce of **20 per cent. argyrol** twice a day. Erosions and ulcerations should be **cauterized** every 3 or 4 days with **silver nitrate,** 10 per cent. to 15 per cent.

DETERMINATION OF A CURE

In cases of acute gonorrhea, it is usually quite easy to decide when a cure has been accomplished; in chronic gonorrhea, the decision is much more difficult. In fact, scarcely any two authorities agree as to the procedure to be followed or the facts to be relied upon in determining a cure.

Up to a few years ago, clinical evidence was all that we had to rely upon to decide whether or not gonococci were still present. Experience has shown that such evidence was very often insufficient, to say the least. Very often, the over-cautious physician has forbidden a man to marry when he was perfectly fit to do so, just because a few shreds persisted in the urine or a non-infectious discharge occasionally appeared. On the other hand, others were allowed to marry who later infected their wives, with results that need not be dwelt upon.

To-day, bacteriology has supplied us with certain tests, which when performed by competent bacteriologists, and considered in conjunction with the clinical evidence, gives us an exact method in deciding this important question.

Clinical Facts.—In view of the prevalence of gonorrhea, it may be accepted, as a general rule, that whenever there is an urethral discharge or pus in the urine, gonorrhea should be suspected. On the other hand, if the urine is free from pus and shreds, gonococcal infection in all probabilities does not exist.

Thus, if a patient continues to have pyuria and is subject to relapses of urethral discharge, he is in the majority of cases still infectious. If he is not subject to relapses after sexual or alcoholic excesses, in all probability he is no longer infectious, even if, at times, a slight discharge is present or shreds appear in the urine.

If, after having had gonorrhea, there is no discharge, pyuria or relapses and no pus can be detected in the urine voided after massage of the prostate and vesicles, one is certainly safe in pronouncing a cure. The presence of shreds in the urine does not signify the presence of gonorrhea. Many men have shreds in the urine who have never had gonorrhea.

The writers employ the following routine in deciding whether or not a patient is cured.

1. **Provocative Test.**—*Technic.*—The urethra is dilated with an antero-posterior Kollmann dilator after which a one per cent. silver nitrate instillation is made in the interior and posterior urethra. The patient is then provided with glass slides to collect the resulting discharge for microscopic examination.

2. The next day the prostate and vesicles are thoroughly massaged upon a full bladder. If any secretion is expressed, part of it is caught on a glass slide and stained, the remainder is transferred to a culture tube. The patient is then told to void into a sterile bottle. The urine after massage is then examined for gonococci and also cultured.

3. **Examination of Condom Specimen.**—Whenever possible a condom specimen of the semen should be obtained and stained and cultured for gonococci.

4. **Complement-fixation Test.**

GONOCOCCAL INFECTION IN THE FEMALE

Occurrence.—The prevalence of gonorrheal infection in women varies within wide limits according to different observers. This great difference of opinion may be accounted for in several ways, viz.: (1) the difficulty of finding the organism in chronic cases, (2) the class of

Practice of Medicine—Tice.

☛ These new pages 513, 514 take the place of the old pages 513, 514, Vol. III. Take out the old, insert the new.

patients treated. In prostitutes, for example, one would expect to find gonorrhea most prevalent. Among 533 prostitutes examined by Huber, 59.6 per cent. had gonorrhea. Among 407 prostitutes, Prowe found gonorrhea in 76.6 per cent. In private practice, Zweifel estimated that the number of women ill because of the gonococcus ranged from 10 to 11 per cent. According to Taylor, the gonococcus is the causative factor in 12 per cent. of all uterine disease.

Gonococcus infection is not uncommon in little girls, especially in institutions.

Organs Invaded.—The urethra, vulva, vagina, cervix, uterine canal and tubes are usually affected. Destructive inflammation of the tubes and ovaries with involvement of the peritoneum is very common. Ascending infection of the urethra, involving the bladder, ureters and kidneys, is by no means rare. Invasion of the rectum may also occur.

Skene's glands and Bartholin's glands frequently become the seat of a chronic gonorrhea. When the ducts of the latter are involved, they appear as two small reddened spots which have been called the "maculæ gonorrhoicæ" of Sänger.

In systemic gonorrhea the same organs are invaded as in the male.

Symptoms and Clinical Course.—The incubation period varies from two to seven days. The disease begins most frequently in the urethra. Skene's glands, lying just within the urethral meatus, and Bartholin's glands, just at the entrance of the vagina, are favorite sites of infection. The vagina lined with pavement epithelium becomes infected, although less frequently than the urethra. In the young, the vaginal mucosa is more easily infected, because the epithelium is softer and more like columnar epithelium. This accounts for the frequency of vulvovaginitis in children.

The next situation most commonly involved is the cavity of the terine cervix. The disease is very prone to become chronic here, just s in the glands of Bartholin and Skene.

The symptoms of gonococcal invasion of the genital organs in women ay be severe or mild.

In severe cases, it is characterized by burning and smarting on urinaon. Within a few hours, the discharge appears at first mucoid, but on becomes purulent. The pus, as in the male, may become greenish-ellow and mixed with blood. The onset of invasion may be ushered by a chill, rapid pulse and an elevation of temperature.

More frequently, the symptoms of invasion are not pronounced. Usuly there is smarting on urination and an increase of the vaginal disarge. Sometimes the only history one can obtain is that of an irriting leucorrheal discharge. Sometimes the symptoms of invasion are mild, that the first symptoms which the patient notices are due to lvovaginal abscess, salpingitis or cervical inflammation.

In the chronic cases, the vaginal discharge although usually profuse, es its purulent character. The symptoms will depend upon the sites infection. These may be the urethra, cervix, tubes and peritoneum, or ene's or Bartholin's glands.

Diagnosis of Gonorrhea in Women.—In the acute form the diagnosis is established by (1) history of suspicious intercourse, (2) clinical symptoms, (3) finding of the gonococcus in the discharges.

In subacute and chronic cases, the diagnosis is more difficult. It rests on a history of coitus, followed by frequent and painful urination and profuse vaginal discharge. Sometimes these are so mild or transient that they escape notice. Questioning the husband will sometimes elicit the statement that at some time prior to marriage he had gonorrhea.

The presence of the "maculæ gonorrhoicæ" of Sänger is strong presumptive evidence of gonorrhea. The redness persists for a long time after all active inflammation has ceased.

In examining a woman for gonococcal infection, it is important that she should come for examination without previous douching or cleansing of the genitals. She is placed in the dorsal position and examined in a good light. Smears are made from the discharge from the vulva and from the orifices of Skene's and Bartholin's glands.

The finger is then passed into the vagina with the palmar surface upward and the urethra is stroked from above, downward and forward, and any secretion that is expressed is collected on a slide. A speculum is next inserted into the vagina and a smear made from the cervical discharge.

Frequently, after a thorough examination, it is impossible to obtain bacteriological confirmation of the disease when the clinical evidence is strongly presumptive of its presence. It should be remembered that the gonococcus is most easily found just after the menstrual period. In doubtful cases, repeated examinations should be made at this time.

Treatment of Gonococcus Infection in Women.—In the acute stage, **rest in bed** and **strict cleanliness** should be insisted upon. The **diet** should be bland and free from spices and stimulants. **Water** should be freely drunk. The bowels are kept free by the frequent use of **saline purgatives.**

For frequent and painful urination, the **citrate of potash and belladonna** mixture are given. **Sandalwood oil,** preferably in capsules, is also indicated.

The genitals are flushed, at least three times a day, with 1 per cent. **hot boric acid solution.** A sterile pad of soft absorbent gauze should be worn constantly over the vulva. When it becomes soiled, it is burned and a fresh one applied.

Local treatment is not begun until the acute inflammation has subsided. The number of drugs recommended for the local treatment is legion. The writers have obtained the best results with **argyrol** 20 per cent., **protargol** 2 per cent., and silver nitrate 1 to 10 per cent. The local treatment must be thorough and persistent. The patient, having emptied her bladder, is placed in the dorsal position in a good light. The vulva is cleansed with cotton sponges dipped in warm water and then wiped with dry cotton. If urethritis is present, ½ ounce of 20 per cent. argyrol or 2 per cent. protargol is injected into the urethra through a soft rubber catheter, the eye of which lies just within the meatus. This solution is retained until the next urination.

A Sims' speculum is next inserted into the vagina, which is thoroughly cleansed and wiped dry. Two per cent. **silver nitrate** is applied to the cervical canal with cotton wound around slender applicators. The vaginal fornices receive the same attention. A **vaginal suppository** containing 10 per cent. argyrol or 2 per cent. protargol is then inserted, after which a cotton tampon is introduced to retain the silver salt. At the end of 48 hours, the patient removes the tampon and takes a cleansing douche of warm water, just before the next treatment.

In the declining stages of the urethritis, silver nitrate is more efficacious than argyrol or protargol. Applications of 2 per cent. silver nitrate are made to the urethra through an endoscopic tube. The silver is next applied to the orifices of Skene's and Bartholin's glands. In sensitive patients, the pain may be lessened by first applying 5 per cent. **novocain, aposthesin** or **cocain** and waiting five minutes before applying the silver.

In chronic cases, where Skene's glands are the seat of chronic infection, they are injected with 1 per cent. silver nitrate, through a hypodermic needle, the point of which has been dulled. In obstinate cases, and where the openings of the ducts have become stenosed, it is necessary to lay them open. A fine probe is passed through the duct the full length of the glands, and the tissues are then divided over the probe. The gland is then **cauterized** with 10 per cent. silver nitrate or destroyed by **fulguration.** The glands of Bartholin, if involved, receive the same attention. If abscess of these glands forms, it should be opened and the interior cauterized.

The vagina sometimes becomes congested and sore after several local treatments have been given. When this occurs it is best to make several treatments with **tampons soaked in glycerin and ichthyol** (12-1) or **boroglycerid.**

In rebellious cases, Kelly recommends the use of **iodoform powder** dusted on dry elastic non-absorbent cotton tampons, so placed as to moderately balloon out the vagina. The packing is done every third day. The patient removes the tampons on the night of the second day and takes a **douche of permanganate of potash 1:1500.**

The treatment of gonococcal infections of the uterus, tubes, ovaries and peritoneum involves **surgical procedures** for the consideration of which the reader is referred to special works on this subject.

Determination of a Cure.—The question is often asked, whether gonorrhea can be cured in a woman. The consensus of opinion seems to be that when the infection is limited to the vulva and urethra and does not extend beyond the cervix, cure is possible after careful and persistent treatment. When the gonococcus invades the endometrium, and the uterine adnexa and adjacent peritoneum, practically all authorities are agreed that the possibilities of a cure are very uncertain indeed. Although many of these patients are apparently cured and discharged as such, experience has shown that relapses may occur.

Before discharging a case as tentatively cured repeated examinations, just after the menstrual period, must show:

(1) Absence of profuse purulent vaginal discharge.

(2) Absence of purulent discharge from Skene's and Bartholin's glands.

(3) Absence of urethral discharge.

(4) Negative smears and cultures.

(5) Negative complement-fixation test.

GONORRHEAL VULVOVAGINITIS IN CHILDREN

Occurrence.—The prevalence of this infection among children is estimated in the various clinics as follows: Sara Welt-Kakels observed, in her clinic at Mount Sinai Hospital, 191 cases of vulvovaginitis during the ten years from 1893 to 1903, representing 1.6 per cent. of all the children treated. The largest number occurred between the ages of 2 and 5 years. After the tenth year the disease was rare. Dr. Flora Pollock, of the Johns Hopkins Hospital Dispensary, reports 139 cases in a series of 1,366 patients. Of these only three cases were congenital, the rest being acquired infections.

It is believed that adhesions of the labia and prepuce, occlusion of the hymen, diseased uterine tubes and deformed uteri are the sequelæ of this disease. The complications are acute peritonitis, arthritis and ophthalmia.

Etiology.—Soiled linen, infected towels or hands soiled with discharges from the mother or father infected with the disease, are the usual carriers of the infection.

Overcrowding and unhygienic surroundings predispose to its transference. Epidemics may occur in institutions, hospitals, asylums and nurseries, due either to ignorance of the nature of the discharge or carelessness in handling it.

Many individual cases are due to rape, due to a superstition among the lower classes that the disease can be cured by coitus with a healthy person, preferably a virgin.

Pathology.—The vagina and vulva are involved. The inflammation is most pronounced at the vaginal outlet, around the hymen, where the pus passes over the perineum.

Symptoms.—The incubation period is from 3 to 4 days. The child may complain of burning on urination and pain on walking, or the mother notes a discharge.

Locally, a profuse purulent discharge is seen pouring out of the vagina. The labia majora are usually reddened and swollen. Excoriations of the integument surrounding the vulva and on the inner sides of the thighs may be present. In cases due to rape, there may be considerable evidence of traumatism.

Diagnosis.—The disease must be differentiated from non-specific vulvovaginitis. due to uncleanliness, urine or rectal worms. These conditions occur most frequently in hot weather. Non-specific vulvovaginitis may occur in the course of measles and scarlet fever. The gonococcus is present in the discharges and its recognition establishes the diagnosis in specific cases.

Treatment.—The mother should be informed of the nature of the disease and of the danger of conveying it to other members of the family. Strict attention should be paid to **cleanliness.** All cloths and dressings should be sterilized by boiling, or should be burnt.

In the acute stage, where there is swelling of the vulva and profuse discharge, the child should be **kept in bed.**

The vulva is copiously flushed three times a day with either **hot boric acid** solution or **1-2000 potassium permanganate.**

If there is much vaginal involvement, irrigations of the vagina are advised, by some gynecologists, with the above-mentioned solutions. These can be given through a soft rubber catheter 12 Fr., gently inserted through the opening of the hymen, after the vulva has been thoroughly irrigated. Personally, we prefer the injection of about 4 to 6 c.c. of **20 per cent. argyrol** freshly prepared.

The degree of vaginal involvement may be determined by inserting a small endoscopic tube into the vagina, with the child in the knee-chest position. In this way the vagina can be examined and the cervix examined for discharge.

In infants, if, after wiping the vulva dry, pus continues to pour out when the child strains or cries, it denotes that the vagina is involved. After flushing the vulva, the parts should be gently dried and an absorbent dressing applied. To protect the skin from irritating discharges, an ointment is applied. **Zinc oxid** or a **3 per cent. protargol** ointment will be found useful.

From time to time, the discharge is examined for gonococci and active treatment continued until they disappear.

In the subsiding stages of the disease, the argyrol is replaced by **instillations of 1 per cent. silver nitrate,** administered three times a week. If erosions persist in the cervix or vagina, they may be touched up with silver nitrate 3 to 5 per cent., through an endoscopic tube or a Kelly No. X speculum. If the urethra is involved, it should be injected daily with **10 per cent. argyrol.**

Whatever the treatment, it should be persisted in until the discharges are free from gonococci. When this occurs, a complement-fixation test is performed. If negative, the case is discharged as tentatively cured.

As the disease has a tendency to recur, the child should be examined from time to time, during the year following.

BIBLIOGRAPHY

ASCH. Modern Treatment of Gonorrhea in the Male, 1915.

BIER. On hyperemia, cited by BAETZNER, W. Zur Behandlung der Arthritis Gonorrhoica der grossen Gelenke mittels Stauungshyperamie. Deut. Ztschr. f. Chir., 1908, xciii, 46–79.

BUSCHKE. Ueber Exantheme bei Gonorrhoe. Arch. f. Derm. u. Syph., 1899, xlviii, 181–204; 385–398.

BYERS. Gonorrheal Ocular Metastases. Montreal, 1908.

CLAPP, C. A., AND MARTIN, M. G. Use of mercurochrome as a germicide in ophthalmia neonatorum. Jour. Am. Med. Assn., May 1, 1920, p. 1224.

COLE, R. I., AND MEAKINS, J. C. The treatment of gonorrheal arthritis by vaccines. Bull. Johns Hopkins Hosp., 1907, xviii, 223.

CORBUS, B. C., AND O'CONNOR, V. J. Diathermy. A specific for gonorrheal epididymitis. Jour. Urology, August, 1924, xii, p. 139.

DORNE, M., AND STEIN, I. F. The mercurochrome ointment treatment of vulvovaginitis. Bull. Chicago Med. Soc., Dec. 15, 1923.

FINGER. Zur pathologischen Anatomie und Klinik der Prostitis Blennorrhagica chronica. Internat. klin. Rundschau, 1893, vii, Nr. 7, p. 259.

GEIRINGER. Urethroscopy, Operative Therapeusis, 1915, V.

GREENE-BROOKS. Diseases of Genito-urinary Organs. 1917.

GUITERAS. Urology, 1912, II.

GUYON. Annales, 1898, xvi, 892.

IRONS. Treatment of gonococcus arthritis by injections of dead gonococci and the clinical reaction which follows the injections. Jour. Infect. Dis., June, 1908, v, No. 3, p. 279.

JOHNSON. Operative Therapeusis, 1915, Vol. V, Chap. IV.

KELLY. Medical Gynecology, 1909.

KEYES. Urology, 1917.

KUSTNER. Lehrbuch der Gynakologie, 1904, p. 389.

LOFARO. La presenza del gonococco nel sangue circolante dei blenorragica. Policlinico, Rome, 1911, xviii, 49.

NEISSER. Zentralbl. f. d. med. Wissensch., xvii, 497.

REED. Diseases of Women, 1913.

ROGERS, J., AND TORREY, J. C. Treatment of gonorrheal infections by specific antiserum. Jour. Am. Med. Assn., Sept. 14, 1907, xlix, 918.

SCHWARTZ AND MCNEIL. The complement-fixation test in the diagnosis of gonococcal infections. Am. Jour. Med. Sc., 1911, cxli, 693.

TEAGUE AND TORREY. Studies from the Dept. of Path., Cornell Univ., N. Y., 1907.

VON HOFFMANN. Bakterienbefunde bei chronischer Gonorrhoe. Centralbl. f. Harn u. Sex. Org., 1904, xv. 41.

VON LACKUM AND HAGER, B. H. Mercurochrome—220 as a valuable adjuvant to the silver compounds in the treatment of gonorrhea and its complications. Jour. Am. Med. Assn., Dec. 8, 1923, p. 1940.

WATSON. Gonorrhea and Its Complications.

WRIGHT. Studies in Immunization. London, 1909.

YOUNG, HUGH H., WHITE, E. C., WHITE, E. O. Further clinical studies on use of mercurochrome as a germicide. Jour. Am. Med. Assn., July 9, 1921, p. 93.

☛ These new pages 519, 520 take the place of the old pages 519, 520, Vol. III. Take out the old, insert the new.

Practice of Medicine—Tice.

CHAPTER XVIII

RABIES

By Eugene R. Whitmore, B.S., M.D.

Definition, p. 521—Synonyms, p. 521—Etiology, p. 521—Epidemiology, p. 524—Mechanism of the disease process, p. 525—Symptomatology, p. 526—Diagnosis, p. 530—Treatment, p. 535—General prophylaxis, p. 534—Prophylactic treatment, p. 535—Treatment of the developed attack of rabies, p. 544—Prognosis, p. 545—Pathology, p. 545—History, p. 547—Geographical distribution, p. 548.

Definition.—Rabies is an acute infectious disease, transmitted by the bite of an infected animal, and characterized by a condition of increased nervous system excitement followed by paralysis.

Synonyms.—Hydrophobia; Lyssa.

Etiology.—In ancient times it was well known that rabies was transmitted by the bite of a rabid animal; and it was later shown that the virus was contained in the saliva. The virus was shown to be present in the salivary glands—especially the submaxillary glands—and in the central nervous system. This virus was studied by a large number of persons; and Pasteur developed the method of protective inoculation before much was known about the virus.

The rabies virus belongs to a group of viruses which pass through bacterial filters, hence the designation "filterable virus." Some of these viruses are cell parasites, and the infected cell reacts by the production of a substance which appears in the cell: these are the viruses to which Prowazek gave the name "chlamydozoa"; that is, cloak-bearing. Further, some of these viruses, when transmitted from the animal in which they commonly occur to another animal and carried through a number of passages in the animal, will not produce disease when inoculated back into the animal from which they came; but produce immunity to infection in the natural way.

This last characteristic of the rabies virus gives the names of "street virus" and "fixed virus," as used by Pasteur.

Pasteur used the term "street virus" to designate the rabies virus that is transferred under natural conditions from dog to dog, from dog to man, or from dog to some other animal.

When this "street virus" is inoculated into rabbits, and is carried from rabbit to rabbit by subdural injection of material from the central nervous system, the virulence of the virus for the rabbit gradually increases; and the incubation time becomes shorter and finally becomes very nearly constant. Thus, "street virus" injected subdurally into a rabbit will kill the rabbit in about 18 days: as the virus from this rabbit is injected into another rabbit, and so on, the incubation time gradually shortens, until the rabbit develops rabies regularly in eight days. This shortening of the incubation period means that the "fixed virus" produces a stronger toxin than does the "street virus"; and in keeping with this, the central nervous system becomes infectious in less time after inoculation with "fixed virus" than after "street virus," indicating higher virulence in the "fixed virus."

For us, the great advantage of the "fixed virus" is that, when injected subcutaneously, it is not infectious for man, and it is far less infectious than "street virus" for dogs, monkeys and other animals; and, when so injected, it produces immunity against infection with "street virus."

The year 1903 gave us important additions to our knowledge of the rabies virus: as Remlinger demonstrated the filterability of the virus, and Negri discovered, in the pyramidal cells in the central nervous system, the bodies that bear his name.

Negri bodies are round or oval bodies, varying greatly in size, from 1 to 27 microns in diameter: in the dog they are usually from 4 to 10 microns in diameter. The number of these bodies in a nerve cell varies from one to five or six. The bodies are found in the ganglion cells in the central nervous system: so, they are found wherever these cells are found. On account of the abundance of ganglion cells in the hippocampus (Ammon's horn), the Negri bodies are most numerous there; but they are also found in the Purkinje and pyramidal cells in the cerebellum, in the cerebral cortex, in all parts of the brain, and in the nerve cells in the spinal cord.

While Negri bodies are numerous and large in the central nervous system of animals dead of "street virus," they are much smaller and are not so numerous following inoculation of "fixed virus." Frosch has suggested that the reason for this is that the shortening of the incubation period does not give time for the bodies to develop.

The Negri bodies are found in the central nervous system of animals infected with rabies; and they are never found in any other animals. By differential staining, the Negri body is seen to consist of 1 to 20 or 30 dots that stain deep blue or black with methylene blue, embedded in a hyalin matrix that stains magenta with eosin. In sections of the brain, the bodies are always intracellular, and contain the dots, known as "inner bodies." When examined in the fresh state, the Negri body appears as a homogeneous mass of ground substance, packed full of coccus-like granules.

While there is agreement that the Negri bodies are characteristic of rabies, there is difference of opinion as to what the bodies are. Negri was of the opinion that the bodies were protozoa; and some authorities hold that view, and consider the "inner bodies" to be granules of chromatin. Others hold that the bodies are reaction products of the infected cell, and that the virus itself is not seen. Lentz describes the formation of the mass of ground substance from the substance of the infected cell. The third and most commonly held view is that the "inner bodies" are the virus, while the mass of ground substance is a reaction product from the infected cell. Koch considers the "inner bodies" to be the virus in the form of the coccus-like bodies, and the ganglion cells being more resistant than the other cells, encapsulate the virus with a layer of degenerated cytoplasm.

In some early work, Pasteur noted numerous fine granulations in the central nervous system of animals dead of rabies; and he suggested that these granulations were the virus of rabies. Since that time, numerous workers have studied these granulations, without being able to determine what they are. These fine coccus-like points are found irregularly throughout the substance of the central nervous system, especially in the gray matter. They are also found in the salivary glands. Koch suggests that these coccus-like bodies are the virus of rabies.

The rabies virus in the brain is protected from the action of physical and chemical agents; and this has led to a belief that the virus is unusually resistant to unfavorable influences. However, Poor and Steinhardt have compared the virus from the brain with that from the salivary glands, filtered through a Berkefeld filter, and they conclude that the virus is actually more resistant than many known organisms. Galtier showed that the virus remained alive in the brain of a dog that had been buried 44 days. At — 4° C. (24.8° F.) it remains virulent as long as 34 months. The virus is rapidly reduced in virulence by air, light and drying; but there is difference of opinion as to whether this is simply an attenuation of the virus or actual killing of the virus, and in that way reducing the dose of the virus in a given amount of material. By Pasteur's method of drying the cord, the virus completely loses its virulence in 10 to 15 days. Harris has shown that freezing and drying in vacuo does not decrease the virulence of the virus to any extent. *In vacuo*, in the dark, the virus retains its virulence for 30 days at a temperature of 23° C. (73.4° F), and 20 days at 35° C. (95° F.). It is killed in 1 to 4 hours at 45° C. (113° F.), in 1 hour at 50° C. (122° F.), in half an hour at 52° to 58° C. (125.6° to 136.4° F.), and in 5 minutes at 60° C. (140° F.). The virus is not affected by 33 per cent. neutral glycerin in 80 days; and this is a satisfactory method of preserving the virus: the glycerin kills the contaminating bacteria, so such material can be used for inoculation of animals for diagnosis. The Negri bodies are well preserved in the 33 per cent. glycerin solution. The virus is killed by chemical agents as follows: 1:1000 solution of bichlorid of mercury, in 2 to 3 hours; 1 per cent. phenol solution in 2 to 3 hours; and formaldehyd vapor in 40 to 45 minutes.

The rabies virus diffuses through glycerin, and even through normal tissues that have been immersed in glycerin containing rabies material. From this diffusibility, and its behavior on filtration, Remlinger suggests that the rabies virus may be considered as intermediate between the smallest visible organisms and the enzymes. The rabies virus passes through the placenta, from the mother to the fetus, as has been shown in the cases of the human, dog, sheep, rabbit and guinea pig.

Various attempts at cultivation of the rabies virus have been made, and some successful cultivations have been reported; but none of the cultures have been carried beyond the stage of purely scientific interest.

The rabies virus produces a toxin which seems to be partly bound to the nerve tissue. Rabies material filtered through a Chamberland filter produces emaciation, paralysis and death in experimental animals; but the central nervous system of these animals is not infectious. Galtier found that the rabies toxin was capable of producing paralysis even after heating to 100° to 105° C. (212° to 221° F.).

Epidemiology.—Rabies in man and lower animals is the result of inoculation of the virus through the bite of rabid animals; and the dog is peculiarly adapted to spread the infection. The disease occurs among all warm-blooded animals; but the dog and cat families are the ones most commonly affected. Some birds are occasionally infected with rabies; but these do not play any part in the spread of the disease.

From his habits, the dog is the common transmitter of rabies to other animals and to man. This results from the fact that the dog goes and comes as he pleases, and comes in close contact with man. The long teeth of a dog, making a deep or torn wound, make infection more common after dog bites. In some frontier regions, the wolf plays a part in the spread of rabies; and the fox may also transmit the infection. In India, jackals are quite frequently infected; and they transmit the infection to dogs, and not infrequently to man. Of 569 persons treated at the Pasteur Institute at Shillong (Assam) in 1917, 97 had been bitten by rabid jackals. Coyotes and skunks are frequently infected in the western part of the United States; and they transmit the infection to dogs and not infrequently to man. Cats are rather frequently infected, though the disease in them is apt to be of the paralytic form. Cattle are rather frequently infected, as are horses; but these animals do not so readily transmit the infection to man, partly because they do not come in such close contact with him, and partly because their teeth crush rather than puncture or tear when they bite. Goats, sheep and pigs are not infrequently infected, and they may transmit the infection to man. Rats and mice are also often infected with the virus; but it does not appear that they play any part in the spread of rabies or in the infection of man. Schmitter observed a case of rabies in a wild monkey in the Philippines.

So, for practical purposes, it may be considered that the dog is the animal responsible for the spread of rabies, as is indicated by the eradication of the disease from England and the prevention of its entrance into Australia as a result of preventive measures directed against the dog as the transmitter. Also, the dog is far the most important transmitter of the disease to man, as is shown by Dobert's tabulation of rabies in Prussia. From 1903 to 1907, 1069 rabid animals injured, mostly by bites, 1817 persons: 1025 (94.1 per cent.) of these animals were dogs; 37 (3.4 per cent.) were cats; 15 (1.4 per cent.) cattle; 6 (0.6 per cent.) horses; 1 (0.1 per cent.) sheep; and 4 (0.4 per cent.) hogs. There is only one case reported in which it seems practically certain that the infection was transmitted from person to person; though, naturally, a number of persons have received some minor wound, or have gotten the patient's saliva on their skin, while caring for cases.

There is no evidence of the transmission of rabies in any other way than through the saliva of the infected animal—generally by a bite, at times by the rabid animal licking the hand of a person, the virus being licked into some abrasion on the skin. Slight abrasions may suffice for inoculation of the virus; and it is not necessary that the bite be deep. There is no proof that the infection is transmitted by meat or milk from infected animals, and there is no proof of its transmission by coitus. Remlinger could not produce rabies in guinea pigs by instillation of an emulsion of a highly virulent virus into the conjunctival sac; but he succeeded in producing rabies in about one of four or five attempts by instilling a small amount of an emulsion of the virus into the nasal cavity, taking great care not to injure the mucosa.

The saliva of an animal may be infective as long as three days before symptoms develop. On the other hand, it is often difficult to demonstrate the infectivity of the saliva even after the symptoms of rabies have developed.

SUSCEPTIBILITY to rabies varies in different animals. In the lower animals, it is usually considered that 40 to 70 per cent. are susceptible, while man is much less susceptible. Thus, some authorities put the susceptibility of man as low as 5 per cent., while others put it as high as 50 per cent. The danger of infection varies with the number and the severity of the bites. Multiple bites and deep lacerated bites are more likely to transmit the infection than are the crushing bites of horses and cattle. There is more danger of infection when the virus is inoculated by a bite on the uncovered skin than when through the clothing. Subcutaneous injection of the virus produces rabies in about 50 per cent. of experimental animals; and with a virus of high virulence for the guinea pig, Remlinger says that subcutaneous inoculations frequently fail.

While it is generally considered that rabies is more common in the summer months, statistics of the disease in Germany do not bear out that belief. In Seattle, an outbreak of rabies began in September, 1913, and there were 361 cases of canine rabies in the city to June, 1914.

There is no difference in age or sex susceptibility. However, children from 6 to 15 years old are more commonly bitten, and boys are more commonly bitten than are girls. This seems to be dependent entirely on the habits of children, playing in the streets and fields and making no effort to avoid a strange dog.

Mechanism of the Disease Process.—When rabies virus is naturally or experimentally introduced into the body of the animal, it travels to the central nervous system along the nerves or through the blood and lymph. It is generally held that along the nerves—possibly in the lymph spaces in the nerves—is the usual route of the virus; through the blood and lymph channels being unusual. Section of the spinal cord prevents the passage of the virus from the leg to the brain, and the part of the central nervous system nearest the bite is the part that shows the first evidence of the virus. In the same way is explained the longer incubation period when a person is bitten on the leg or arm as compared with a bite on the face—that is, closer to the brain. On this basis, the virus reaches the salivary gland by traveling down the nerve from the brain. The authorities who hold the view that the virus travels along the nerves are of the opinion that the long incubation period is, in great part, at least, represented by the time it takes the virus to travel along the nerves to the central nervous system.

Koch is of the opinion that the virus spreads through the blood and lymph channels very generally; and that this is probably the more common way of spread of the virus in the body. On this basis, the virus is picked out from the blood especially by the nervous tissue, whether it be in the central nervous system or in the salivary glands. The virus is present in the blood of a rather small percentage of animals at the time of death from rabies; but it is undetermined whether the frequent presence of the virus in the suprarenals, and the less frequent presence in the spleen and pancreas is from a primary infection of the blood or from a secondary infection of the blood from the central nervous system.

According to Fermi, the rabies virus passes through the unbroken mucous membrane of the nose, conjunctiva and intestine, in fifteen minutes. When inoculated into the anterior chamber of the eye, it takes the virus twenty-four hours to reach the outside of the eyeball. Immediate cauterization of the wound does not surely prevent rabies; but half the experimental animals are saved when the bite is cauterized within thirty minutes. This rapid passage of the virus is considered by some authorities to favor the opinion that it travels by the blood and lymph channels. The authorities who hold the view that the virus commonly travels in the blood or lymph channels are of the opinion that the long incubation period is due to the virus remaining for some time in the central nervous system before it has multiplied enough to produce symptoms.

The lesions of rabies are due to the toxin produced by the virus. Babes is of the opinion that the disturbances of the nervous system, including paralyses, following prophylactic inoculation with rabies virus, are due to the toxin of the rabies virus. Babes considers that the leukocytosis, that is present even before symptoms appear, accounts for the plugging of the capillaries and the small areas of softening in the brain.

Since animals rarely or never recover from rabies, nothing is known regarding immunity following an attack of the disease. The mechanism of immunity following antirabic vaccination is discussed under vaccination in this article.

Symptomatology.—A. RABIES IN LOWER ANIMALS.—The clinical picture of rabies is in general the same in all susceptible animals; and, since the dog is the lower animal in which the diagnosis has usually to be made, it is best to discuss the symptoms of the disease in the dog. While the symptoms vary somewhat, as a result of age, sex, race and temperament, it is possible to distinguish two varieties: the *furious rabies* and the *dumb* or *paralytic rabies;* and each variety is marked by three stages: the prodromal stage, the stage of excitement, and the stage of paralysis.

Incubation Period.—The incubation period varies greatly; being on the average from five to eight weeks in natural infections. Haubner gives the incubation period as less than two months in 83 per cent. of his cases, 16 per cent. within three months, and the remaining 1 per cent. in the fourth month or later.

In experimental rabies the incubation period is shorter, partly because a larger dose of virus is injected than in natural infection, and partly because the virus is in a more concentrated form and is injected directly into the central nervous system. The average incubation period, when the virus is injected into the muscles of the lumbar region, is about seventeen days; when the virus is injected subdurally, it is from ten to fifteen days. Konradi reports one case where a rabbit died of rabies thirteen months after subdural inoculation of brain emulsion from a child dead of rabies.

1. *Furious Rabies.*—In the *prodromal stage,* the dog shows a change in disposition: a good-natured, playful dog appears dejected, and slinks away into a dark place. In other cases, the dog is unusually friendly, and even a vicious dog may be friendly: in such cases the dog may show a disposition to lick his master's hand; and, as the saliva is already infectious, there is danger of infection through any cuts or abrasions on the skin of the hands. At times the dog may act normal, or be unusually active; and this state may alternate with periods of dejection and slinking. The animal may start at any sudden noise. The site of the bite is often irritated, and the dog may lick it.

An important thing in this stage is the abnormal appetite: the dog does not care to eat his food, but he will swallow all sorts of material, as sticks, stones, hair, leather and dirt. This must be kept in mind in the postmortem examination of a dog suspected of having had rabies.

The *stage of irritation* is the period that gives the name of "mad dog" to the rabid dog. One of the most important signs is that a dog that is never in the habit of leaving home will run away; and the dog may travel miles, never getting back home, or returning worn out with running, and with his coat full of dirt and his flesh torn from fighting with other dogs. Many times the dog snaps at and bites everything it comes near; and such a dog may run among a group of persons and bite a number of them before it runs on in its mad rush over the world.

A change in the bark is said to be characteristic: the bark changes to a hoarse howl.

After two to four days, the dog develops weakness in the hind legs and hips, and passes into the *paralytic stage.* The dog appears weak, staggers as he walks, and may fall. This weakness may extend to the front legs, and to the muscles of the jaw. At times the jaw is affected first: the lower jaw hangs down, and bloody froth flows from the mouth: the dog cannot bite, and raises the head with difficulty. There is great emaciation, with profound weakness; and death follows.

Duration.—The prodromal stage lasts about one or two days; the stage of excitement two to four days; and the paralytic stage one to two days. The entire course of the disease, after symptoms appear, is usually five or six days; never more than ten days.

II. *Dumb or Paralytic Rabies.*—In this form of rabies, the *prodromal stage* and the *stage of excitement* are short, and may be overshadowed by the *paralytic symptoms* from the start. There is often increased excitability, but the weakness makes it impossible for the dog to run, and there is not the furious running through the country, such as is seen in the stage of excitement in the furious type of rabies. The weakness may begin in the jaw; and "jaw drop" may be one of the first things noticed. The weakness rapidly spreads to the body, and the dog is soon not able to walk or stand. He lies quietly, the body being shaken from time to time with short muscular cramps.

It would appear that the paralytic rabies is merely a severe form of rabies, as it is common in experimental rabies when the inoculation is into the muscles, and it is the form that is seen in the rabbit following inoculation of fixed virus. But at times dogs with paralytic rabies live longer than dogs with furious rabies; though it may well be that the average duration of paralytic rabies is shorter than the average duration of furious rabies.

Under natural conditions, about 80 to 85 per cent. of dogs develop furious rabies, and about 15 to 20 per cent. develop paralytic rabies.

B. Rabies in Man.—The forms and stages of rabies in man are the same as those in the dog, except that the furious form is represented by a spasmodic form.

Incubation Period.—The incubation period varies even more in man than it does in the dog. The minimum incubation period observed is twelve days. Kozewaloff observed 212 cases of rabies in man: the incubation period was 20 to 40 days in 40.6 per cent. of the cases; 40 to 60 days in 25 per cent. of the cases; 12 to 20 days in 13.7 per cent.: that is, the incubation period was less than 60 days in 79.3 per cent., and over 60 days in 20.4 per cent.; in 3.8 per cent. the incubation period was over 200 days, 3 cases over a year, and one case over two years. Koch says that the rabies virus may lie dormant in the nervous system for a long time, and be roused by trauma, fatigue, emotional stress or abuse of alcohol.

The long incubation period and the great variation in the length of the period in man probably depends on several factors. One of the most important seems to be that man is not very highly susceptible to the rabies virus. Other factors are the virulence of the virus; the depth, size, number and location of the bites; and the age of the patient —children are more susceptible than are adults. Ordinarily there are no symptoms during the incubation period; though there may be some anxiety, probably due to fear of the development of rabies.

I. *Spasmodic Rabies.*—Rabies in man does not take the furious form that is so common in dogs; but rather takes a spasmodic form, such as is not infrequently seen in guinea pigs in experimental rabies.

In the *prodromal stage,* there is often irritation in the scar of the bite; this irritation amounting to itching or pain, with redness or edema. There may be neuralgic pains in various parts of the body. The patient has headache, and there is loss of appetite. The important symptoms are psychic in nature: the patient is depressed and anxious, and cannot sleep. The voice is often changed, especially in children, to a peculiar whine.

At times the *stage of excitement* sets in suddenly, without any prodromata. More commonly it is preceded by prodromata. The first characteristic symptom is the spasm of the muscles of deglutition, making it difficult or impossible to drink water, and giving the feeling of something in the throat. This spasm of the muscles of deglutition is a prominent feature throughout the course of the disease; and the patient early develops a fear of trying to drink, on account of the painful spasms in the throat—hence, the name "hydrophobia." But the fear of water may be absent throughout the disease. The irritability increases until the slightest stimulus, as the sight or mention of water, a draft of air, a noise, a bright light or even a touch, brings on the severe spasms of the muscles of deglutition. Spasm of the muscles of respiration comes on early; and there is precordial distress. The special senses are hyperesthetic.

These spasms come on in the form of attacks, which do not last more than half to three-quarters of an hour. An attack is often induced by the slightest irritation. Beginning with spasm of the muscles of deglutition, the spasm spreads to include certain groups of muscles, as those of respiration; or there may be generalized convulsions. These convulsions may be mild or severe, being even tetanic in character. It is possible to see the spasm of the muscles in the throat; and a little saliva or mucus is frequently expelled from the lips as a result of this spasm. The peculiar sound that has been likened to the barking of a dog is due to spasm of the muscles of the larynx. There is dyspnea; and the patient may die suddenly in one of these attacks. The spasm of the muscles, extending to the muscles of the jaw, gives rise to the peculiar chewing or snapping movements that have been considered to resemble the biting movements of the rabid dog. The abundant salivary secretion may be churned to a froth by the spasm of the jaw muscles. There is great anxiety, which may be increased to a sort of mania, with delusions and hallucinations. The patient shudders; springs from his bed, and rushes to the door and about the room; clutches at his throat; gets on all fours and grovels on the floor; and, when restrained, begs to be allowed to go.

Between attacks, the patient is quiet, and his mind is clear; though there is great anxiety. Even during the attacks, the patient is conscious, and tries to avoid injury to those who are caring for him. Allen and Horne report a case where a child with rabies bit her father on the hand; but it is not clear whether it was an accidental bite as a result of the father trying to relieve the child's suffering during one of the spasmodic attacks.

There is fever of 100° to 107° F. (38° to 42° C.); and high terminal temperature, such as is met with in a number of other conditions (as delirium tremens) may occur. Nausea and vomiting are common; the vomitus frequently being blood stained. In the beginning, the pulse is full and bounding, but later it becomes weak and rapid, especially during the attacks. The urine is decreased in amount, and does not contain albumin; but it may contain sugar.

The patient may die suddenly, in a convulsion or from asphyxia, during one of the attacks; or the attacks may become more frequent, and the patient dies from exhaustion. More commonly, when the patient does not die during one of the attacks, he passes into the *paralytic stage;* the spasms stop, and there is great weakness and paralysis. The cessation of the spasms makes it possible for the patient to drink water, and the respiration is quiet; so there may be an appearance of improvement. But the paralysis increases, and the patient passes into coma and dies.

Duration.—The prodromal stage may last three or four days, or it may be entirely absent; and the feeling of something in the throat and the inability to drink may be the first signs of the disease. Death does not occur in the prodromal stage.

The stage of excitement lasts from one to four days; usually two or three days. Death is frequent in this stage from apoplexy; in a convulsion; or from asphyxia, suddenly, or after a short period of agony.

The paralytic stage does not last over two to eighteen hours, and death is in coma.

The average duration of the disease, from the time the spasms of the throat set in, is two to three days.

II. *Paralytic or Dumb Rabies.*—Just as with the dog, the prodromal stage and the stage of excitement may be very short, and the paralytic symptoms predominate from the start. Children and persons severely bitten, as by wolves, seem more liable to develop dumb rabies.

Diagnosis.—The mortality in human rabies is 100 per cent., but it is possible to prevent development of rabies in man in over 95 per cent. of the cases by prophylactic inoculation after the person is bitten. This indicates the great importance of prompt diagnosis of rabies in animals; the dog being the animal that is all important in transmission of rabies to man.

CLINICAL DIAGNOSIS OF RABIES IN DOG.—A *clinical diagnosis* of rabies in the *dog* is practically impossible, owing to the other conditions that may simulate rabies. The history of the dog is important. One of the most important signs is that a good-natured, playful dog becomes cross, and slinks away into a dark place; or a cross dog becomes affectionate. The dog may leave home and travel for miles; then return home, emaciated, tired and torn from fighting. In the nature of things, it is difficult to find evidence that a dog was bitten by some other animal.

When a dog is suspected of being rabid, it should not be killed, but should be shut up and observed for ten days. If, at the end of that time, the dog remains well, it may be considered that the dog was not rabid.

LABORATORY DIAGNOSIS OF RABIES IN DOG.—When a suspected rabid dog dies or is killed, the brain should be examined, since a *laboratory diagnosis* is the only way in which a satisfactory diagnosis can be made. In killing the dog, care should be taken not to crush or shatter the brain, as this leads to rapid contamination with bacteria and the brain will very soon be unsuited for animal tests. If the examination has to be made at a laboratory that is some distance away, the dog's head should be cut off and sent to the laboratory, packed in ice. If it is necessary to send the head some distance for examination, and it is not possible to pack it in ice, the brain may be removed carefully and sent in 33 per cent. glycerin in water; or it may be packed in borax.

1. *Stomach Findings.*—In the examination of a dog for rabies, it is very important to examine the stomach and its contents. If the dog's stomach contains normal stomach contents, and the small intestine contains normal intestinal contents, the probability is that the dog did not have rabies. On the other hand, if the dog's stomach contains sticks, stones, leather and other indigestible matter, it is probable that the dog had rabies. It is necessary to be careful not to make a diagnosis of rabies on the finding of foreign substances in the stomach, as it is not uncommon for dogs to have masses of foreign matter—especially hair—in the stomach. In one case of suspected rabies in a pup, a mass of excelsior was found in the esophagus at postmortem, and it was difficult to say whether it was the result of the perverted appetite of a rabid dog or an accident to a playful pup. It is necessary to be very careful in interpreting the appearance of submucous hemorrhages in the stomach.

2. *Microscopical Examination of Brain.*—(*a*) *Direct Examination for Negri Bodies.*—In examining a brain for rabies, a direct microscopical examination for Negri bodies should be made. If the information obtained from this direct examination is not satisfactory, animals should be inoculated with the brain substance. At the same time some of the brain tissue should be preserved in neutral glycerin in the ice-box, for further animal inoculations in case of accident to the first set of animals. Possibility of accident must be guarded against in every way, in cases where the dog has bitten some person, as every day lost in making a diagnosis increases the patient's danger of contracting rabies in case the dog was rabid.

The brain is carefully removed from the skull, and parts of it taken for examination for Negri bodies. As the Negri bodies are in the large ganglion cells, it is necessary to take parts of the brain in which these cells are most numerous. For this reason the hippocampus major (Ammon's horn) is usually taken; though Negri bodies can be found in the pyramidal cells in the cerebral cortex and in the Purkinje cells in the cerebellar cortex. There is less danger of confusion from other cell inclusions when material is taken from the hippocampus or the cerebral cortex for examination.

Smears of the brain substance are examined, and if the information is not satisfactory, sections are cut and examined. If this examination does not give satisfactory information, some of the brain substance may be injected into guinea pigs or rabbits.

There are numerous *methods of staining smears* and section for Negri bodies; but any one of the methods will give satisfactory results. The *Lentz method* is preferred for diagnosis, as it gives clean-cut differential staining of the Negri bodies; and it is also possible to prepare stained sections in less than three hours by this method.

Technic of Lentz Method of Staining.—A thin transverse slice of tissue through the hippocampus is spread between two slides by gentle pressure and drawing apart of the slides. Without allowing them to dry, the slides are placed in methyl alcohol for ten minutes, and are then washed in a mixture of absolute alcohol and ether. For the staining, five solutions are used: (1) A 0.5 per cent. solution of water-soluble eosin in 60 per cent. alcohol; (2) Loeffler's methylene blue solution; (3) Lugol's solution; (4) five drops of a 1 per cent. solution of sodium hydrate in absolute alcohol added to 30 c.c. of absolute alcohol; and (5) one drop of 50 per cent. acetic acid solution in 30 c.c. of absolute alcohol. All of the solutions keep well, but the alkaline alcohol must be free of water.

For sections, a transverse slice of the hippocampus, not over 2 mm. in thickness, is placed in acetone in the incubator at 37° C. for one hour, then in paraffin in the incubator for one hour; embedded and thin sections cut.

Stain in the eosin solution for one minute; wash in water; stain in Loeffler's methylene blue one minute; wash in water; mordant with Lugol's solution one minute; wash in water; differentiate in methyl alcohol until the specimen is red; wash in water; stain with Loeffler's methylene blue solution half a minute; wash in water; blot dry with filter paper; differentiate in alkaline alcohol until only a faint tinge of eosin is left; differentiate until only the ganglion cells appear faint blue under the microscope, the background of the specimen appearing faint pink; wash quickly in absolute alcohol. Smears are examined direct with oil immersion lens; sections are carried through xylol and mounted in balsam.

The Negri bodies appear crimson in the pale blue cytoplasm of the ganglion cells, the inner bodies being stained dark blue to black. The red cells are stained vermillion and cannot be mistaken for Negri bodies.

Williams' Method of Staining.—Williams makes smears from the cerebral cortex, Ammon's horn and the cerebellum. The partly or completely air-dried smears are fixed for about ten seconds in methyl alcohol (that has been neutralized by the addition of about 0.25 gram sodium carbonate to 500 c.c. of the alcohol) with 0.1 per cent. picric acid. The staining solution is 0.5 part saturated alcoholic solution of basic fuchsin and 10 parts of saturated alcoholic solution of methylene blue, in 30 parts of distilled water. The staining solution is kept in the ice-box, as it deteriorates rapidly at room temperature. The stain is poured on the smear and held over the flame until it steams. The smear is then washed in tap water and blotted with filter paper. The Negri bodies appear magenta color, the nerve cells blue, and the red blood cells yellow or salmon color.

Heidenhain's Hematoxylin Stain.—While Lentz's stain is satisfactory for diagnosis, it is not suited for study of the finer structure and for demonstration of the coccus-like granules in the central nervous system and in the salivary glands. The material is fixed in sublimate alcohol, and is stained with Heidenhain's hematoxylin, with a light counter-stain of eosin. The coccus-like granules appear as black points surrounded by a narrow clear zone, scattered through the tissue in regular groups.

(*b*) *Inoculation Tests with Brain Emulsion.*—If the examination for Negri bodies does not give satisfactory information, some of the brain tissue (preferably medulla oblongata) may be emulsified in physiological salt solution and injected into animals. Rabbits are commonly used, though a number of laboratories use guinea pigs. The latter are more susceptible to rabies than are rabbits, and the incubation period is shorter. Drawbacks to use of guinea pigs are that the disease is irregular in the pig, and not infrequently the pig dies in a few hours from the time it shows symptoms; so a second passage may be necessary to insure a diagnosis. The disease is regular in rabbits. Remlinger advises the inoculation of a pig and a rabbit with the brain emulsion; or the inoculation of a pig, and when the pig dies, the inoculation of a rabbit from it. A number of laboratories recommend the rat for diagnosis of rabies, on account of its greater resistance to infection with contaminating bacteria which may be present in the suspected material, and also because it is less likely than the rabbit to die of intercurrent disease.

If the brain tissue being examined is fresh and free from contamination, it is best injected subdurally or intracerebrally, through a small trephine opening. If the brain tissue is contaminated, it is necessary to inject it into the muscles of the back, or even subcutaneously, as subdural injection would kill the animal. Guinea pigs may be inoculated in the muscles at the nape of the neck or the thigh. The incubation period in the rabbit is 12 to 21 days, though it may be 4 to 6 weeks; and experimental animals should be kept under observation for two months. The incubation period is commonly under 20 days in the guinea pig.

Subdural or intracerebral inoculation is the best, as it gives 100 per cent. of positive results; injection into the muscles on both sides of the spinal column gives 95 per cent. of positive results, while subcutaneous injection gives only about 50 per cent. of positive results.

In rabbits, rabies is usually of the paralytic form, though there are convulsions at times. Furious rabies is rare in rabbits, but it does occur. Street virus usually causes paralytic rabies in the guinea pig. The animal dies in 2 to 4 days after the beginning of symptoms; and the brain is examined for Negri bodies, as was the dog's brain in the beginning.

It is generally considered that production of a disease typical of rabies, by the injection of emulsion of brain, is sufficient evidence on which to base a diagnosis of rabies. However, search should always be made for Negri bodies in the brain of the experimental animals. Several observers have reported diseases which resembled rabies, but which could not be identified as rabies. The "Pesta de coçar," or "Molestia de Aujeszky," reported by Carini and Maciel, appears to be a specific disease which, if it is not rabies, does not deserve to be called pseudo-rabies.

Diagnosis in Man.—In man, the diagnosis of rabies must be made from the history and the clinical picture. A history of being bitten by a dog a month or two before—especially if a stray dog—together with irritation of the site of the bite, is strong indication of rabies. But one must be on guard against lyssophobia: in the latter case the stigmata of hysteria are present. Tetanus, delirium tremens and drug poisoning need only to be kept in mind to differentiate. Rabies is not uncommonly very irregular in man, and the disease may be confused with poliomyelitis or meningitis. The syndrome of Landry's paralysis should always make one think of rabies. The paralyses of the antirabic treatment are of the type of Landry's paralysis. There is an early leukocytosis in rabies. Negri bodies are found in the brain of man in about 40 per cent of the cases; so it is frequently necessary to inoculate animals to make the diagnosis.

Treatment.—GENERAL PROPHYLAXIS.—More than 90 per cent. of all cases of rabies in the human are due to dog bites; and the disease is kept in existence by the canine family. For this reason, measures directed against the *source of the infection* are primarily directed against rabies in the dog. Muzzling of dogs, destruction of stray dogs, and a high dog tax are the measures to be enforced.

In the Department of the Seine, the measures for the control of the disease in dogs consist in destruction of all stray dogs and a dog tax. The amount of canine rabies was greatly reduced, and rabies in man ceased to exist. Since the recent war began, there has been some increase in the number of persons applying for Pasteur treatment, possibly as a result of difficulty in keeping up a strict enforcement of the measures for control of dogs.

In England, rabies has been eradicated by strict enforcement of the order for muzzling dogs. Before 1890, the number of cases of human rabies increased to such an extent that muzzling of dogs was enforced;

the result being that the number of cases fell markedly in the next three years. As a result of opposition to muzzling, the order was not so strictly enforced in the next three years, with the result that at the end of that three years the number of cases of human rabies had increased to twice what it had been before the period of muzzling. Muzzling was again enforced, with the result that the number of cases of human rabies decreased markedly, until, in 1900, there were no cases of human rabies in England. After an absence of about twenty years, rabies has reappeared in England, probably as a result of relaxation of regulations during the war.

In regions where wolves, jackals, coyotes, foxes and skunks play a part in the spread of the infection, special efforts at their destruction are necessary.

Personal Prophylaxis.—It is important to avoid being bitten by, or having abrasions soiled by the saliva of, rabid animals. If necessary to work with a rabid animal, or to make a postmortem examination of an animal dead of rabies, it is necessary to wear gloves, and to see that there are no abrasions on the skin. Attendants on cases of human rabies should wear gloves and see that they have no skin abrasions.

Since rabies has a mortality of 100 per cent. in man, it becomes of the greatest importance to prevent the disease. When a man is bitten by a dog, it is necessary to consider the possibility of rabies, and to treat the man according to whether or not the dog is rabid. The fundamental principle is that, unless it is possible to satisfactorily determine that the dog was not rabid, the man should be treated as though the dog was rabid.

Prophylactic Treatment.—Prophylactic treatment consists in local treatment of the wound and general treatment in the form of immunization against rabies. The wound is always to be treated as though the dog was rabid—unless it is immediately evident that the dog was not rabid—since it is not possible to wait to treat the wound until the condition of the dog is determined. The wound is to be thoroughly cleaned with an antiseptic solution, it being opened freely to the bottom and all shreds of torn tissue trimmed away. The wound should be encouraged to bleed. Of great importance is a thorough cauterization with nitric acid, which seems to have a specific action on the rabies virus. It has been shown that it is possible to prevent rabies in about 40 per cent. of experimental animals by applying a tourniquet above the wound and cauterizing the wound with nitric acid. A simple dressing should be applied.

History of the Dog.—Whether the bitten person shall be immunized must depend on the determination of whether the dog was rabid; and the *history of the dog* and the conditions under which he bit are of great importance in determining this. If the man was accidentally bitten when playing with the dog, or was bitten when teasing the dog, or was bitten by a known vicious dog, it is not necessary to begin immunization; but the dog must be kept under observation for ten days. On the other hand, if the man was bitten by a stray dog that ran up and bit him without provocation and ran on, or by a known dog that shows signs of being sick and, especially, becomes cross, it is necessary to consider beginning immunization at once.

A couple of examples will illustrate how the history may or may not be of value in determining whether the dog was rabid. A stray dog ran among a group of soldiers, snapping right and left, and bit five of the men; then it ran on and began jumping and biting at the noses of a team of horses until the driver got down from the wagon and killed the dog. Under such conditions, the men should have been immunized at once; but the virus was not available, and one man died of rabies a month or two later. In another case, an old dog that had been a house dog and a pet for years was taken sick, without any signs of change of disposition, and without any definite signs as to what was the trouble, except that there was trouble in swallowing. The owner, who was a physician and familiar with rabies in the ordinary form, called a veterinarian; and the veterinarian repeatedly placed his hand in the dog's mouth to examine for anything there might be in the throat. The dog never showed any signs of snapping or biting, and the children cared for the dog until its death. Negri bodies were found in the brain of the dog; and animals inoculated with brain substance of the dog developed rabies. On finding the Negri bodies, the children were immunized; but the veterinarian decided not to be immunized. No one developed rabies.

Indications for Antirabic Vaccination.—It is necessary to carry out antirabic vaccination in every case where there is a chance that the person has been inoculated with rabies virus; at the same time it is desirable not to submit the person to the treatment unnecessarily. On this account, different workers have formulated lists of *Indications for Antirabic Vaccination;* Heller and Rothermundt give the following indications, with a table from Marie and Remlinger:

1. If a man is (*a*) bitten by a dog, (*b*) has the uncovered skin soiled with froth or saliva, or (*c*) is scratched by the dog, it is not necessary to give antirabic vaccination if the dog is known, or is observed promptly and shows no disturbance, provided it is known that there has been no rabies in the region for six months. If there is rabies in the district, it is advisable to start antirabic vaccination at once, and to continue it until the dog can be observed for ten days.
2. All other cases are handled as follows:

1. If the dog dies in less than ten days after biting the man.	Antirabic vaccination should be carried out.
2. If the dog is killed in less than ten days after biting the man.	
3. If the dog disappears.	
4. If the dog is unknown.	

5. If the dog is living and is observed for ten days.	1. Develops rabies. 2. Dies under suspicious circumstances.	Antirabic vaccination should be carried out.
	3. Is sick, but lives over ten days.	The dog should be observed further, and antirabic vaccination carried out if he develops rabies.
	4. Remains well at the end of the ten days' observation.	Antirabic vaccination should not be carried out.

In all cases where the dog is killed or dies under suspicious circumstances, it is important to have the brain examined for Negri bodies, and to have animal inoculations carried out, in case the microscopic examination of the brain should not furnish the satisfactory information.

Development and Methods of Antirabic Vaccination.—In 1881, Galtier immunized sheep against rabies by giving them intravenous injections of the saliva of rabid dogs. But Pasteur's work placed antirabic vaccination on a practical basis. Based on the results in small-pox vaccination, Pasteur considered it possible to attenuate the virus of rabies, and to produce immunity with that attenuated virus. His first experiments were carried out by passing the virus through monkeys, and using the spinal cord from these monkeys for immunization of dogs. He began his treatment with cord from a monkey injected with a virus that had been through a number of passages in monkeys, and for each succeeding injection used a virus of shorter passage, until he reached a virus that had been only once through a monkey.

From his success with this method of immunization, Pasteur simplified the method by using rabbits instead of monkeys; and he attenuated the virus by drying it for different lengths of time. He began treatment with a cord that had been dried for a number of days, and used a cord that had been dried a shorter time, until the final doses were with a cord that had been dried only three days.

As Pasteur's method of antirabic vaccination came to be used in numerous laboratories, various modifications of the method were developed.

Högyes held that Pasteur's method did not attenuate the virus, but that it diluted the virus, in that the virus died out gradually during the drying. On this basis, Högyes used undried cord, beginning with a dilution in such a dose that it would not cause rabies when injected into an animal, and gradually increased the dose.

Other laboratories attenuated the virus by heat, by the action of artificial gastric juice, by the action of glycerin, and by the action of 1 per cent. carbolic acid solution.

The method was further modified by injecting serum of an immunized animal at the time the virus was injected, or by mixing the immune serum with the virus and injecting the mixture.

Ferran's method is of interest, in that it demonstrates that man stands large doses of undiluted and unattenuated fixed virus, without developing rabies. Ferran gave large doses of undiluted and unattenuated fixed virus subcutaneously.

Other methods are of scientific interest but not of practical importance.

Various workers showed that the injection of normal nervous tissue produced immunity against rabies; but Marx held that this was not a specific immunity, but only a non-specific increased resistance.

Where dried or attenuated virus is used, it is usual to inject constant or varying lengths of cord, beginning with the longer dried, or more attenuated, and gradually increasing to the more virulent cord. The following table may be taken as the type of this form of treatment:

Day of treatment	Amount of cord	Age of cord	Day of treatment	Amount of cord	Age of cord
1	2 c.c.	3 days	12	2 c.c.	1 day
2	2 c.c.	2 days	13	2 c.c.	3 days
3	2 c.c.	1 day	14	2 c.c.	2 days
4	2 c.c.	1 day	15	2 c.c.	1 day
5	2 c.c.	3 days	16	2 c.c.	1 day
6	2 c.c.	2 days	17	2 c.c.	3 days
7	2 c.c.	1 day	18	2 c.c.	2 days
8	2 c.c.	1 day	19	2 c.c.	1 day
9	2 c.c.	3 days	20	2 c.c.	1 day
10	2 c.c.	2 days	21	2 c.c.	1 day
11	2 c.c.	1 day			

In the case of severe bites, this course may be repeated in a month. This treatment is intensified in some institutes by giving two injections a day for five or six days in the beginning.

The Public Health Service begins with 8-day dried cord, and reaches a 3-day dried cord on the second day of the treatment. Children receive a smaller dose of the shorter dried cord than do adults.

Where the Högyes dilution method is used, it is usual to inject varying amounts of different dilutions of the ground-up cord, beginning with a high dilution, and gradually increasing to the stronger suspensions. The following table will serve as a type of this form of treatment:

Day of treatment		Dilution	Amount in cubic centimeters
1 day	morning	1:10,000 + 1:8,000	3 — 3
	afternoon	1: 6,000 + 1:5,000	3 — 3
2 day	morning	1: 5,000	3
	afternoon	1: 2,000	2
3 day	morning	1: 2,000	2
	afternoon	1: 1,000	1½
4 day	morning	1: 1,000	1½
	afternoon	1: 500	1
5 day	morning	1: 200	1
6 day	morning	1: 6,000 + 1:5,000	3 — 3
	afternoon	1: 2,000	2
7 day	morning	1: 2,000	2
	afternoon	1: 1,000	1½
8 day	morning	1: 1,000	1½
	afternoon	1: 500	1
9 day	morning	1: 200	1
10 day	morning	1: 6,000 + 1:5,000	3 — 3
	afternoon	1: 2,000	2
11 day	morning	1: 2,000	2
	afternoon	1: 1,000	1½
12 day	morning	1: 1,000	1½
	afternoon	1: 500	1
13 day	morning	1: 200	1
14 day	morning	1: 100	1

For severe injuries, or injuries about the head, this course is often intensified by giving more and stronger emulsions, and by continuing the injections for 20 days.

In some laboratories serum from rabies-immune animals, usually dogs, is used, in addition to the injection of the vaccine. Babes gives a course of vaccine in the regular way, and then gives two doses of 20 c.c. each of immune serum, with one day intervening between the doses. Marie uses a mixture of the vaccine and immune serum, in which there is a slight excess of vaccine. The results from this method are entirely satisfactory.

In all methods, the injections are given in the right and left hypochondrium alternately.

With all of the methods, where the bites are numerous or especially severe, or are on the face, it is usual to intensify the treatment by giving more injections, and of more virulent virus, in the first few days of the treatment.

The usual methods of carrying out the antirabic vaccination require that one or more rabbits shall be inoculated every day, in order that there shall always be a supply of virus of the right age available. This is an expensive matter for small laboratories that have only occasional cases to treat. For this reason, there has been effort to develop a method by which it is possible to preserve the virus for some time. Calmette dried the cord the required number of days and preserved it in glycerin, and found that the virulence was retained for twenty-five to thirty days. In this way, cord of proper length of drying can be kept on hand. Calmette did not use cord that had been longer than two weeks in glycerin.

Harris applied Shackell's method of freezing and drying bacteria to the freezing and drying of the rabies virus *in vacuo;* he found that the virus so dried, and kept dry and cold, retained its virulence unchanged for six months. This method of preserving the virus is used in connection with the dilution method of carrying out the antirabic vaccination.

Koch considers that potassium iodid is of value in the prevention of rabies; and every person is given a course of potassium iodid while taking the antirabic vaccination at Koch's Institute in Berlin.

Accidents during Antirabic Vaccination.—In general, there is no inconvenience from the vaccination. The local reaction is not severe, and the patient can be up and around during the vaccination.

Geiger has studied the *local reactions* of the Pasteur treatment. He finds that the local reaction very regularly appears on the seventh and eighth days, and on the fifteenth and sixteenth days. Occasionally a patient will have a reaction every day; and rarely will he have no reaction at all. The reaction consists of an edematous area, with erythema, itching, pain and tenderness. The largest area of local reaction was 10 by 12 cms. Sometimes there is slight general reaction, in the form of malaise and slight fever. He considers the reaction as due to hypersensitiveness to the nervous tissue injected; but he also notes that the reaction is more marked with the use of high potency virus.

Aside from the persons dying from rabies due to the bite of the animal for which they were being treated, there have been a few cases in which there seems to have been disturbance from the vaccination itself. In over 200,000 persons treated, Simon collected 103 that developed untoward symptoms during treatment, including those who developed rabies from the bite for which they were under treatment. Simon tabulated 100 cases of *paralysis* among 217,774 persons treated. Thus, of the persons treated, 0.048 per cent. developed paralysis.

Fielder collected 142 cases of "treatment paralysis." Cases of paralysis are very rare among persons treated by the Högyes dilution method: 3 cases in 51,417 persons treated, a per cent. of 0.000058.

Mejia tabulates the cases of paralysis among the persons treated at the Pasteur Institute in Buenos Aires. Of 19,800 persons treated, 24 developed paralysis.

The paralysis usually develops about the fifteenth to the twentieth day—not infrequently as early as the eleventh day—after the beginning of antirabic treatment. Mejia used two methods of injection: one in which he gave 26 injections in 19 days, and one in which he gave 19 injections in 11 days. When the shorter course of treatment was used, the paralyses came on the last day of the treatment or the day after; that is, 11 or 12 days after the treatment was started. When the longer course was used, the paralyses came from one day to a week after the last injection; that is, 16 to 20 days after the treatment was started.

One of Mejia's cases of paralysis was a child, 6 years old, which received 26 injections in 15 days. The child was seen one month after completion of treatment, and was entirely well. A few days later, the child received a blow while playing in a hammock, in the morning. That afternoon, the child vomited; and paralysis developed the next day. Apparently the injury was not of such a nature that it could have been the direct cause of the paralysis.

In all of the cases of paralysis, the picture is very much the same. It begins with loss of appetite, mild fever, considerable stiffness in the back and weakness in the legs. This weakness in the legs increases to complete paralysis, and ascends, involving the sphincters of the bladder and rectum. The paralysis may extend upward and involve the upper extremities and the face, and there may be bulbar symptoms. There may be disturbance of respiration and heart action and difficulty in swallowing. Mejia's cases of paralysis were in the form of transverse myelitis, multiple neuritis and ascending paralysis. The picture is frequently that of Landry's paralysis. There may be pain in the scar of the bite for which the person is being treated.

The condition lasts for two or three weeks, and recovery is complete. Remlinger collected 40 cases, of which 38 recovered. Of Simon's tabulation of 100 cases, 81 recovered; in Fielder's tabulation of 142 cases, 118 recovered; and in Mejia's 24 cases, 20 recovered. As these tabulations, especially Simon's, include cases who developed rabies during the treatment, it appears that the mortality among persons who develop paralysis is not over 15 or 16 per cent. In Simon's tabulation, of the persons treated, 0.00812 per cent. died.

It is not easy to explain these paralyses, and it has been suggested that they are due to various causes, as follows:

1. Abortive cases of the paralytic form of rabies, resulting from the bite for which the person is being treated, which recover under the antirabic treatment.
2. Abortive cases of the paralytic form of rabies, due to the fixed virus inoculated.
3. The toxin of the rabies organism.
4. The toxic action of the material used in the injection, other than the toxin of the rabies organism.
5. Anaphylaxis.

It is possible that the condition may be due to more than one of the above causes. Fielder considers it as generally due to the fixed virus used in the treatment, either a virus infection or the toxin, or both. Fixed virus has been found in the brain of some cases dead of treatment paralysis; in other cases, no rabies virus was found in the brain.

Mejia considers the paralyses are due to the virus itself, and warns against too rapid pushing of the treatment. He says that certain people have an idiosyncrasy, and that some organisms do not react as well as others in the presence of toxic or infectious substances.

The rarity of the condition following use of the dilution method of treatment is important. The possibility of bacterial contamination of the material used for the injection should be kept in mind and guarded against.

Personal idiosyncrasy plays an important part in the development of these treatment paralyses. The condition rarely affects children. It is to be remembered that persons who have been bitten by a dog are likely to have nervous and hysterical symptoms.

So, it is evident that antirabic vaccination is not without an element of danger, and should not be given unnecessarily.

Contra-indications to Antirabic Vaccination.—There are no contraindications. The treatment is stopped if the patient develops rabies or treatment paralysis during the vaccination. Other diseases, or pregnancy, are not contraindications. There may be relapse of malaria during the vaccination, but it is to be treated in the usual way.

Availability of Antirabic Vaccination.—Commercial firms and Boards of Health throughout the country prepare the vaccine for antirabic vaccination and send it out in syringe containers, ready to inject: full instructions accompany each package of vaccine.

Results of Antirabic Vaccination.—The probability of failure of antirabic vaccination depends on a number of factors. The nearer the bite is to the central nervous system the greater the danger, as with wounds on the face or head; wounds on uncovered parts of the body are more dangerous than where the bite was through clothing; the number and extent of the bites are of importance; the most dangerous bites are, in descending order, those of wolves, jackals, cats, dogs and other animals. Of 569 persons treated at the Shillong Pasteur Institute in 1917, 5 died of rabies—4 of these being bitten by jackals; and of 4 failures of the antirabic vaccination, 3 were bitten by jackals. One jackal was reported to have bitten as many as thirty people. It is to be remembered that a dog, in licking a wound, or soiling it with froth from the mouth, may inoculate with rabies; and there seems to be some indication that superficial wounds and abrasions are apt to be dangerous, possibly because they usually get no local treatment at all. Of less importance is the age of the person, antirabic vaccination being more likely to fail with young persons than with older persons.

Of great importance is the length of time after the bite before the beginning of the protective vaccination. Where the wounds are severe, and a period of ten days has elapsed since they were received, it is not possible to prevent rabies by antirabic vaccination. Where the patient comes late for treatment, it is possible to give an intensive course of treatment, and thus lessen the danger of failure; but in many such cases the virus has already spread in the nervous system and the vaccination fails. In addition to this, there are cases in which the treatment is begun early and is carried out properly, yet the patient develops rabies. It seems that in such cases there has been a failure on the part of the tissue to elaborate antibodies, just as there may be failure to elaborate antibodies against any infection. In other cases the vaccination merely holds the virus in check, and a shock or injury, perhaps months afterward, may lead to development of rabies.

Using the frozen and dried virus by the dilution method, Harris says the time required for immunization is shortened over the Pasteur method by more than half. He collected reports of 1159 persons who had been treated with the frozen and dried virus by the dilution method. No person developed rabies after fifteen days following the last injection. One died during the treatment and one died 14 days after the first injection. There were no paralyses. The proportion of persons developing paralysis from the dilution (Högyes) method, is about 1 in 17,000.

It is considered that at least 14 days must elapse after completion of the vaccination before the person is immune, and on that basis it is usual to eliminate cases developing rabies during the treatment, or within 15 days after completion of the treatment, in calculating the value of antirabic vaccination.

Not all persons bitten by a rabid animal will develop rabies, the proportion being given as about 1 in 6. Since it is impossible to determine whether a large part of the persons receiving antirabic vaccination were bitten by rabid dogs, it is not possible to say what proportion of the treated persons fail to be protected.

In determining the results of vaccination, the patients are divided into *three classes*, according to the information available as to whether or not the biting animal was rabid:

A. Cases where the biting animal is proved to be rabid by natural or experimental inoculation.
B. Cases in which the biting animal is diagnosed as rabid by a veterinarian. (Certified rabid.)
C. Cases in which the biting animal is suspected of being rabid.

The following table of persons treated at the Pasteur Institute, Paris, in 1916, gives an idea of the results of vaccination in these different classes:

Year, 1916	Treated	Died	Mortality (per cent.)
Class A	188	3	1.59
Class B	658	0	0
Class C	542	0	0
Total	1388	3	0.21

From its establishment in 1886 to the end of 1916, the Pasteur Institute in Paris vaccinated 36,534 persons, of whom 133 developed rabies after an interval of 15 days following the completion of the treatment; that is, 0.36 per cent.

Remlinger collected the statistics of all institutes over varying periods of years; and his table shows that of 152,859 persons vaccinated, 705 (0.46 per cent.) developed rabies after an interval of 15 days following the completion of vaccination. There are great differences in the results from different institutes, the higher percentages of failures probably being where wolf bite is more frequent, where it is difficult for the people to reach the institute, and where the people are careless about prompt treatment.

Immunity Following Vaccination.—The immunity in man, following vaccination, lasts about one year. Williams cites the case of a man who developed rabies 14 months after antirabic vaccination, and 6 weeks after exposure to infection.

Marie found dogs immune 18 months after vaccination. Ravenel states that in dogs the protection has disappeared, at the end of one year in 21 per cent.; at the end of two years in 33 per cent.; while it persists for five years in others.

Mechanism of Immunity.—Fixed virus, injected into man, is killed before it reaches the central nervous system; and the organisms, being broken up, act as antigen and lead to the development of rabicidal substances which circulate in the serum of the vaccinated person. This development of rabicidal substances can be demonstrated in vaccinated animals. There is undoubtedly a tissue immunity, as is found in other immunity reactions, as vaccinated animals are immune after it is no longer possible to demonstrate rabicidal substances in their blood.

Dilutions of virulent material lead to active development of rabicidal substances, while dried, avirulent material leads to the production of a much lower grade of immunity. From this, it appears that the immunity results from the breaking down of the rabies organism itself and not from the rabies toxin. Since it is possible to produce increased resistance to rabies infection with injections of normal nervous tissue, it is necessary to remember that the immunity produced by the dried, avirulent material may be of the nature of a non-specific increased resistance, rather than specific immunity.

Heredity of Immunity.—Exceptionally, in animals, an immune mother transmits immunity to the young through the placenta; but this immunity is never transmitted to the next generation.

TREATMENT OF THE DEVELOPED ATTACK OF RABIES.—The patient should be put to bed and kept there, a restraint apparatus being used if necessary. As any stimulus brings on the spasmodic attacks, the room should not be brightly lighted, and there should be no sudden noises, drafts of air or other sudden stimuli. Generally liquids cannot be swallowed; but semi-solids can often be swallowed. **Ice cream** and **custards** may be taken. When nothing can be swallowed, food may be **given by rectum,** and thirst may be relieved in the same way.

The ordinary sedatives have very little action in controlling the spasms; but it is advisable to give **morphin** hypodermically, in an effort to diminish the severity of the spasmodic attacks. Inhalation of **choloroform** may give relief from the attacks; and **chloral** and **bromids** may be given by enema. **Curare** and **calabar bean** have been recommended, and there are reports of recovery under the use of curare. **Atropin** is advised by some of the authorities in India.

Moon and Harris reported cures of rabies from the administration of **quinin**; Haberlin reported a cure from the injection of **phenol solution** after the manner of Bacelli's method for the treatment of tetanus; and Tonin reported a cure from the use of **salvarsan.** Unfortunately, further trial has not confirmed the value of any of these methods of treatment.

Prognosis.—It is generally held that rabies in man is fatal in 100 per cent. of the cases; and that the reported cases of recovery are cases of lyssophobia. It seems pretty definitely agreed that there are occasional cases of recovery in dogs. While it is possible to transmit rabies to birds—chickens and pigeons—the disease is usually mild, and tends to spontaneous recovery.

The development of rabies in man can be prevented by prompt prophylactic inoculations in over 95 per cent. of the cases bitten.

Pathology.—MACROSCOPIC.—In general, there are no gross changes in the animal dead of rabies. There is emaciation; and there is a catarrhal condition of the mucous membrane of the nose and mouth. There may be no change in the central nervous system. More commonly, the brain and the meninges are congested and edematous, and there may be pin-point hemorrhages and areas of softening in the depth of the brain and cord; the areas of softening in the cord being especially common in man. Not infrequently the spinal cord is softened, especially when the animal has died of paralytic rabies.

The stomach is shrunken, and contains no food; but is filled with foreign substances as sticks, stones, hair, straw, leather and any other foreign substance the dog may have picked up during the period of excitement. There are often hemorrhagic erosions in the gastric mucosa, but this is probably not connected specifically with rabies.

MICROSCOPIC.—In a section of the central nervous system, as the spinal cord, one of the striking things is the blood-vessel changes. The blood-vessels are dilated and packed with red cells; and in places there are minute aneurysms or ruptures of the vessel wall, giving rise to the minute hemorrhages that are seen in the gross specimen. These hemorrhages may destroy the surrounding tissue, and produce the areas of softening. The vessel walls are thickened and are infiltrated with leukocytes; the perivascular lymph spaces being filled with leukocytes. There are hyaline areas in the vessel walls, and some vessels are plugged with masses of leukocytes or fibrin. These changes are especially marked in the anterior and posterior horns and about the central canal, in the spinal cord.

But it is in the nerve cells in the central nervous system that the most striking changes are found in rabies (Fig. 1). The outline of the ganglion cells becomes indistinct; the nucleus is granular and fragmented; the cytoplasm is granular and stains diffusely with eosin, and shows hyaline change. The cell is vacuolated or may contain large spaces; and when the process has lasted some time the cells may be changed to granular, fatty masses. In cases of long duration, there is granular and fatty change in the neuroglia cells. About these degenerated ganglion cells is the same leukocytic infiltration that is found about the blood-vessel walls; and these areas of infiltration about the blood-vessels and the degenerated nerve cells, scattered through the central nervous system, are the "rabies tubercles" of *Babes.*

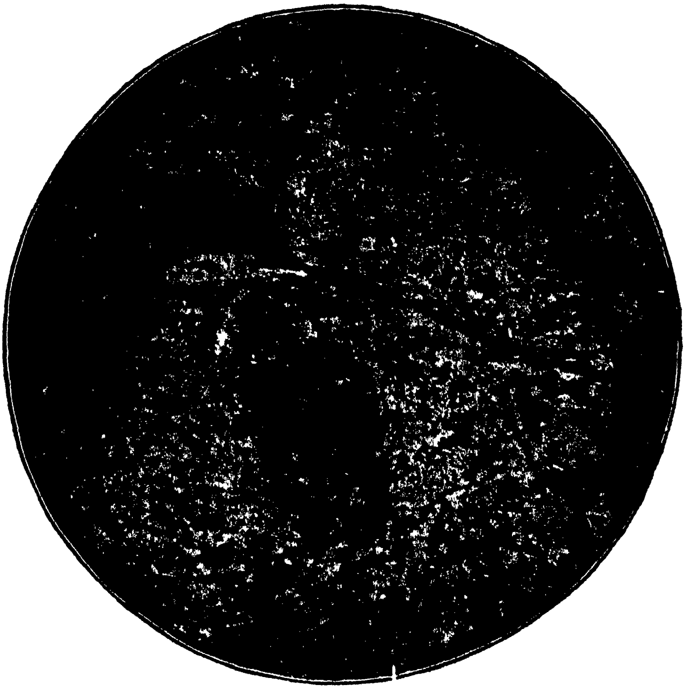


FIG. 1.—RABIES TUBERCLE IN THE MEDULLA. (From Ravenel, in Osler and McCrae's "Modern Medicine," Lea & Febiger.)

The specific finding is the Negri bodies in the ganglion cells in the central nervous system. Manouelian reports the finding of Negri bodies in the cytoplasm of the ganglionic nerve cells in the salivary glands. The gland epithelium degenerates and is taken up by endothelial cells. No Negri bodies are found in the gland epithelial cells.

Lentz described peculiar bodies in the large pyramidal cells in the hippocampus major of rabbits that had been inoculated with passage virus. From their resemblance to Negri bodies, and their presence in the brain of animals inoculated with passage virus, Lentz called them "passage bodies" and considered them specific for passage virus. Other authorities have considered these bodies as degenerated cells, such as are found in rabbits which have been poisoned with diphtheria toxin, and hold that they are not specific.

The change in the central nervous system is inflammatory in nature, and was considered an acute myelitis by Schaffer. Golgi considered it as a parenchymatous encephalomyelitis which combined irritative and degenerative changes. The changes in the nerve cells and neuroglia are due to the action of the toxin formed by the virus, which has a special affinity for the central nervous system.

History.—It is convenient to divide the history of rabies into four periods, the first period going back to ancient times. Akteon, son of Aristeus, died of rabies about 13 centuries B. C. (Yount). The disease was well known in Aristotle's time (26 B. C.), as he writes, "Dogs suffer from madness. It throws them into a state of fury, and all animals which are then bitten are also attacked with madness, with the exception of man": it is quite possible that this refers to the form of the disease, rather than that man was not considered to have rabies. Human rabies was well known at the time of Celsus, in the first century A. D. From this time until 1800 little was added to the knowledge of rabies. Indeed, it was during the latter part of this period that were developed so many of the ideas that still are not entirely dead: Zwingers' idea that a non-rabid dog could transmit rabies to man; and Bosquillon's idea that there was no special rabies virus, but that fear alone could produce the disease. Meads, in 1767, and van Swietens, in 1770, described the paralytic form of human rabies.

The second period began in 1804, when Zinke transferred rabies from an infected animal to another animal, by painting the saliva of a rabid dog onto a fresh wound on another dog, the second dog developing rabies. He also transmitted the infection to a rabbit and to a chicken in the same way. The method of transmitting rabies from dogs to rabbits was developed and, in 1879, Galtier showed that this was a good method of determining whether a dog had rabies; and Raynaud showed that the rabies virus could be transmitted from man to rabbits. In 1826 von Krügelstein expressed the opinion that the rabies virus was in the central nervous system; and Duboué, in 1881, confirmed this finding, and considered that the virus reached the central nervous system by way of the nerves.

The work of Pasteur and his co-workers marks the third period in the study of rabies. Pasteur showed that the rabies virus is constantly in the central nervous system of rabid animals; that subdural injection of small amounts of the brain or spinal cord of rabid animals into susceptible animals constantly produced rabies. He showed that, when the rabies virus from dogs is injected into rabbits, after a few passages the virulence of the virus for the rabbit is increased, until it kills in a short time. This virus no longer produces rabies in dogs, but renders them immune to a subsequent injection of virus from the dog. He applied this method to the immunization of persons bitten by rabid animals; with the results we know to-day.

The fourth period in the history of rabies began in 1903 with Negri's discovery of the small bodies in the ganglion cells in the central nervous system of rabid animals. The regularity with which these bodies are found in the brain of rabid animals makes it possible to make the diagnosis in nine-tenths of the animals that die of rabies, without having to wait for the disease to develop in inoculated rabbits.

Geographical Distribution.—Rabies occurs in all parts of the world, in cold as well as warm climates. It has not been observed in South and Central Africa, and it has not been reported from Siberia, though it is common in Russia. Australia is free from the disease, as a result of exclusion of the disease by rigid quarantine. As a result of rigid quarantine and muzzling of dogs, England was free from the disease for twenty years, but it has reappeared as a result of relaxation in the enforcement of regulations. The disease is fairly common throughout the United States.

BIBLIOGRAPHY

Allen, R. E., and Horne, F. L. Report of a case of rabies in which a child bit her father. Calif. State Jour. of Med., 1913, xi, 408.

Calmette, A. Notes sur la rage en Indo-China. Ann. de l'Inst. Pasteur, 1891, v, 633.

Carini, A., and Maciel, J. Peste de Coçar. (Pseudo-ravia, Paralysia bulbar infectiosa, ou Molestia de Aujeszky.) Brazil Medico, 1912, xxvi, 491.

Cruikshank, J. A., and Wright, R. E. A note on some experiments performed with a view to finding out the period before symptoms when the saliva of an animal incubating rabies is infective. Indian Jour. of Med. Research, 1914, i, 532.

Cumming, J. G. Quinin treatment of rabies. Jour. Infect. Dis., 1914, xv, 205.

Ferenbaugh, T. L. A note on the occurrence of hydrophobia in the foxes of Alaska. Military Surgeon, 1916, xxxviii, 656.

Fielder, F. S. The treatment of human rabies with quinin and with phenol. Jour. Am. Med. Assn., 1916, lxvi, 1300.

——— Paralysis during Pasteur antirabic treatment. Jour. Am. Med. Assn., lxvi, 1769.

Geiger, J. C. Local reactions of the Pasteur treatment and their time of appearance. Jour. Am. Med. Assn., 1916, lxvii, 1518.

Haberlin, J. H. An apparent cure in a case of rabies. New York State Jour. of Med., 1913, xiii, 493.

Harris, D. L. Further studies on the effects of desiccation of the virus of rabies, and the use of this material in immunization. Jour. of Infect. Dis., 1913, xiii, 155.

——— A clinical report of seven cases of hydrophobia, together with a case clinically similar, with recovery following the injection of quinin. Jour. Am. Med. Assn., 1913, lxi, 1511.

——— Comparative results in antirabic treatment. Jour. Am. Med. Assn., 1916, lxvii, 923.

Hasseltine, H. E. Paralysis during antirabic treatment; a report of two cases in which paralysis occurred during the course of antirabic treatment. Public Health Reports, 1913, xxviii, 2220.

Heller, O., and Rothermundt, M. Wutschutzimpfung und Wutimmunität. Handbuch der pathogenen Mikroörganismen, Kolle u. Wassermann, 1913, Bd. viii, 897. Zweite Auflage, Gustav Fischer, Jena.

Janeway, J. G. On hydrophobia. New York Med. Rec., 1875, x, 177.

Jarvis, N. S. A case of rabies from a skunk bite. New York Med. Jour., 1890, lii, 344.

KNOWLES, R. First annual report of the King Edward VII Memorial Pasteur Institute, Shillong, for the year ending December 31, 1917. Printed at the Assam Secretariat Printing Office, Shillong, 1918.

KOCH, J. Lyssa. Handbuch der pathogenen Mikroörganismen, Kolle u. Wassermann, 1913, Bd. viii, 789. Zweite Auflage, Gustav Fischer, Jena.

——— Lyssaforschung. Deutsch. med. Wchenschr., 1913, xxxix, 2025.

KONRADI, D. Hérédíté de la rage. Ann. de l'Inst. Pasteur, 1916, xxx, 33.

LANFRANCHI, A., AND LENZI, F. Sul passaggio del virus rabido dalla madre al feto. Ann. d'ig. sper., 1918, xxviii, 233.

LENTZ, O. Ein Beitrag zur Färbung der negrischen Körperchen. Centralbl. f. Bakteriol., etc., I Abt., Orig., 1907, xliv, 375.

LUZZANI, L. N. Le diagnostic de la rage. Ann. de l'Inst. Pasteur, 1913, xxvii, 907 and 1039.

MANOUELIAN, Y. Récherchés histologiques sur les glandes salivaires dans la rage. Ann. de l'Inst. Pasteur, 1914, xxviii, 233.

MEJIA, C. R. Accidentes paralíticos consecutivos á la vacunación antirábica. Semana méd., 1917, xxiv, 10.

MOON, V. H. The effect of quinin on rabies in dogs. Jour. Infect. Dis., 1913, xiii, 165.

——— Further observations on the effects of quinin in rabies. Jour. Infect. Dis., 1915, xvi, 58.

NEGRI, A. Beitrag zum Studium der Aetiologie der Tollwut. Ztschr. f. Hyg. u. Infektionskrankh., 1903, xliii, 507.

NOGUCHI, H. Contribution to the cultivation of the parasite of rabies. Jour. Exp. Med., 1913, xviii, 314.

OUSHAKOFF, V. G. Hydrophobia: two instructive cases. Russky Vrach, 1914, xiii. (Abs. Jour. Am. Med. Assn., 1914, lxviii, 616.)

POOR, D. W., AND STEINHARDT, E. A study of the virus of rabies freed from the cells of the host and from contaminating organisms. Jour. Infect. Dis., 1913, xiii, 203.

PROESCHER, F. Artificial cultivation of rabies virus. New York Med. Jour., 1914, c, 953.

PUBLIC HEALTH REPORTS: Seattle. Rabies in animals. 1914, xxix, 1639.

RAVENEL, M. P. Rabies. Modern medicine, Osler and McCrae, Vol. I, 2nd Edition, 1913, 956. Lea and Febiger, Philadelphia.

——— Le passage du virus rabique à travers les filtres. Ann. de l'Inst. Pasteur, 1903, xvii, 834.

REMLINGER, P. Contribution a l'étude de la nature du virus rabique. Bull. de l'Acad. de méd., 1918, lxxix, 137.

SCHMITTER, F. Hydrophobia in a wild Philippine monkey. Jour. Am. Med. Assn., 1914, lxii, 598.

SIMON, G. Ueber Lahmungen im Verlauf der Tollwutschutzimpfung. Centralbl. f. Bakteriol., I Abt., Orig., 1913, lxviii, 72.

STIMSON, A. M. Rabies in the United States during the year 1911. Public Health Reports, 1912, xxvii, 1098.

TONIN, R. Un caso d'idrofobia umana guarito col 606. Policlinico, sezione pratica, 1912, xix, 1041.

VIALA, J. Les vaccinations antirabiques a l'Institut Pasteur en 1916. Ann. de l'Inst., Pasteur, 1917, xxxi, 368.

WILLIAMS, A. W. Hydrophobia. Forchheimer's Therapeusis of internal diseases, 1914, Vol. V., 707. D. Appleton & Company, New York.

YOUNT, C. F. Rabies—with report of cases from skunk bites. South. California Pract., 1910, xxv, 117.

CHAPTER XIX

MALARIA

By Charles C. Bass, M.D.

Etiology, p. 551—Predisposing causes, p. 551—Exciting cause: the malaria parasite, p. 564—Morphology and development, p. 564—Distribution of malaria parasites in the body, p. 573—Cultivation of malaria plasmodia, p. 573—Distribution of malaria parasites outside of the body, p. 579—Modes of conveyance, p. 579—Types of infection, p. 584—Symptomatology, p. 584—Clinical history, p. 584—Physical findings, p. 594—Laboratory findings, p. 597—Special examinations, p. 602—Diagnosis, p. 602—Complications and association with other diseases, p. 606—Sequelæ, p. 607—Clinical varieties, p. 610—Treatment, p. 612—Prophylaxis, p. 612—General management, p. 626—Diet, p. 627—Climatology, p. 627—Local treatment, p. 628—Treatment of symptoms, p. 628—Specific therapy, p. 628—Medicinal treatment, p. 628—Surgical indications, p. 632—Management of convalescence, p. 633—Prognosis, p. 633—Pathology, p. 637—Historical summary and distribution, p. 641—Sociological aspect, p. 642.

Etiology.—1. Predisposing Causes.—(1) *Cold, Extremes of Temperature.*—Exposure to extremes of temperature cannot cause infection with malaria, except that possibly such influences may increase the susceptibility to infection of people who otherwise possess a considerable degree of immunity, if such a thing exists. People already infected (malaria carriers, who are sources of infection without themselves having attacks) frequently have attacks of chills and fever or other clinical forms of the disease following sudden chilling of the surface of the body, especially if they are very warm at the time. It has been frequently noted that laborers or other individuals in intensely malarious sections who are infected but present no symptoms at the time frequently begin to suffer from chills and fever as soon as the rainy season sets in, and often considerably in advance of the time necessary for a new crop of *Anopheles* to grow, become infected and transmit malaria. The author was told by Dr. Carter and Dr. James that in the Canal Zone, whenever the rainy season sets in, there is a great increase in the cases of malaria admitted to the hospitals, even in the first week or two. They attributed this to the fact that the laborers are drenched by showers while out at work. The sudden chilling of the body brings on the symptoms. The increase occurs in a much shorter time than is required for an increased crop of mosquitoes to result from the rainy season and for them to become infectious.

(2) *Climate.*—A dry climate is opposed to malaria and a wet cli-

mate favors it. This fact is due to the influence upon the production of *Anopheles.* The longer the rainy season in any locality, the more favorable that locality is for *Anopheles* and, of course, for the transmission of malaria. Generally speaking, the nearer we approach the tropical climate, the greater the intensity of malaria. Though *Anopheles* can withstand a great deal of exposure to cold, even the larvæ passing through quite severe winters, they are not active during cold seasons and therefore a cold climate is opposed to the transmission of malaria. Generally speaking, the longer the cold season, the less malaria, and the longer the warm season, the more malaria.

(3) *Season.*—The season of the year which is the most favorable for the transmission of malaria is the one also most favorable for the development of *Anopheles,* namely, the warm season. In the southern United States the malaria transmission period is from about May 1st to November 1st. The most favorable period of transmission is the entire warm season. It is a fact that there is a greater tendency for infected persons to develop clinical symptoms during the spring and fall than during the summer months, probably due to the greater daily variations in temperature during these seasons. Tertian malaria is much more frequent during the spring and early part of the summer than estivo-autumnal, which is more frequent during the late summer and fall. Clinical attacks of malaria rapidly decrease upon the appearance of cold weather. Usually in the southern states, during the months of December, January and February, there is a great reduction. It is to be supposed that little or no transmission is taking place during this period and that the cases that do develop are relapses. Though there is a great reduction in the cases of the disease at this time, some cases occur even during the coldest season. Malaria mortality by months in the United States registration area is shown in Fig. 1 from Hoffman.[1]

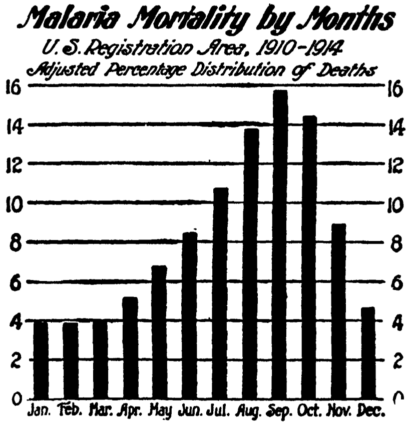


FIG. 1.—CHART SHOWING MALARIA MORTALITY BY MONTHS (Hoffman, Courtesy Prudential Press).

During the past several years the United States Public Health Service has gathered information from the physicians of several different southern states as to the prevalence of malaria from month to month. These have been included in the Public Health Reports and also published as reprints.[2]

A representative chart (Fig. 2) is reproduced here. It is noteworthy that the high point is reached in September in every state.

(4) *Altitude.*—The higher the altitude, the less likely is transmission of malaria to take place. In tropical countries, where the low-lying valleys are notoriously malarious, the high, mountainous country is usually more or less free from the disease. Not only is a high altitude unfavorable for the transmission of malaria, but it also seems to favor recovery from the disease in individuals who are already infected. Perhaps this is the result of the general invigorating effect of the high altitude. Frequently individuals who are infected and have perhaps not shown any symptoms at all in a low, malarious country, promptly have attacks whenever they go to high altitudes. These attacks are, however, usually followed by more rapid recovery and more certain disinfection than takes place in the lower altitudes.

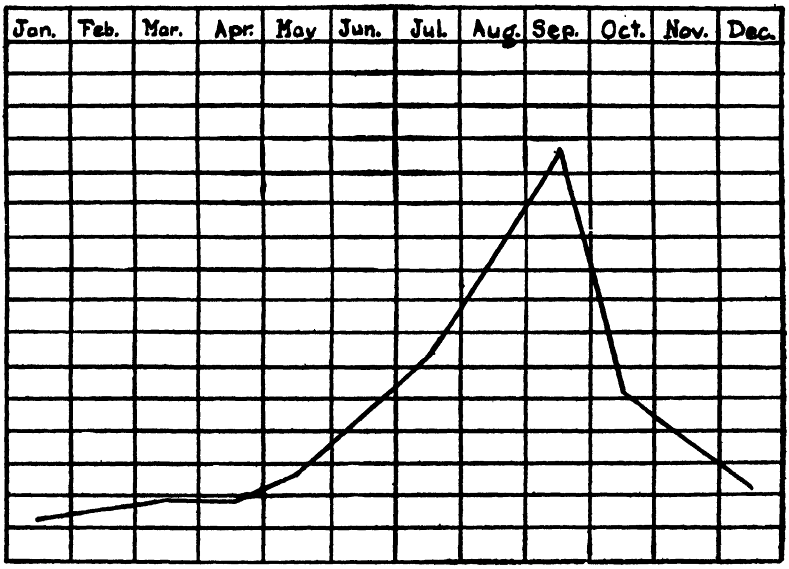


FIG. 2.—RELATIVE PREVALENCE OF MALARIA IN ARKANSAS, BY MONTHS, AS INDICATED BY THE NUMBER OF CASES REPORTED. (U. S. Public Health Report No. 451.)

(5) *Soil.*—The more impervious the soil is to water, the more favorable it is for the production of mosquitoes and therefore for the transmission of malaria. Porous, sandy soil is least favorable for the collection of water in pools, ponds, etc., and therefore least favorable for mosquito-breeding and the transmission of malaria.

(6) *Sex.*—Malaria is slightly more prevalent among males than

among females. Our Bolivar County investigations, including 31,459 persons, showed by blood examination 21.44 per cent. infection in males and 19.83 per cent. in females.

(7) *Age.*—Malaria has been generally thought to be more prevalent in children than in adults. A blood examination of 31,459 persons in our Bolivar County experiments showed this to be the case. The greatest prevalence is reached at the age of six. Fig. 3, taken from the report of this work made to the International Health Board, shows the percentage of infection found in the ages under twenty over a period of two years; and Fig. 4 shows graphically the percentage by age groups.

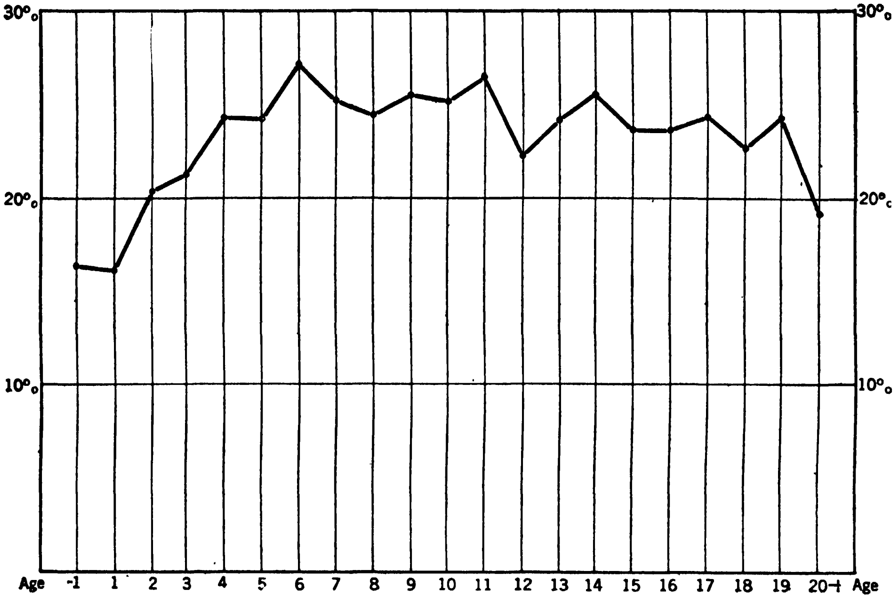


FIG. 3.—BLOOD INDEX BY YEARS, TO 20 YEARS; FIRST EXAMINATION 31,459 PERSONS.

The great importance of malaria to the youth of the country is shown more impressively by Fig. 5, in which the distribution by ages of the total amount of malaria found is shown.

(8) *Race.*—Deaderick[8] says:

"Caucasians residing in non-malarial countries are, when exposed, most liable to contract malaria. Negroes bred in highly malarial regions are, as long as they remain upon their native soil, least susceptible to paludal infection.

"Immunity within the race increases generally as we go toward the equator. Thus the negroes of the Southern States display less immunity than the negroes of the West Indies or of tropical Africa. Likewise it may be said that immunity is much more marked in countries with a high than in those with a low endemic index.

"The immunity of the negro race has been variously estimated, some observers maintaining that they are absolutely proof against ma-

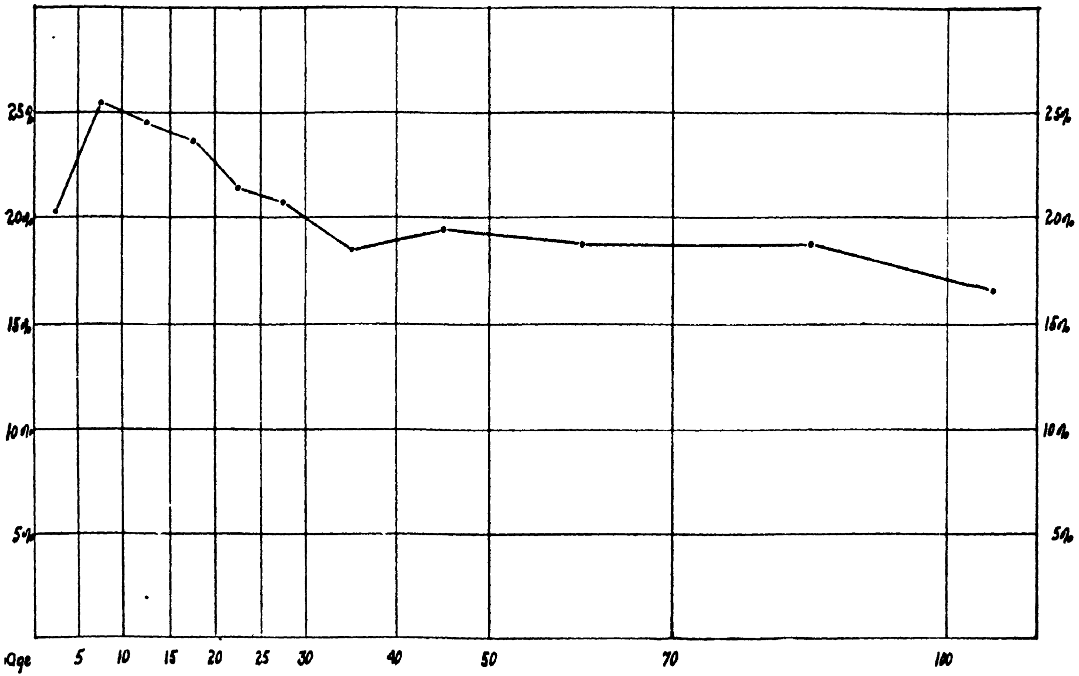


FIG. 4.—BLOOD INDEX BY AGE-GROUPS; FIRST EXAMINATION 31,459 PERSONS.

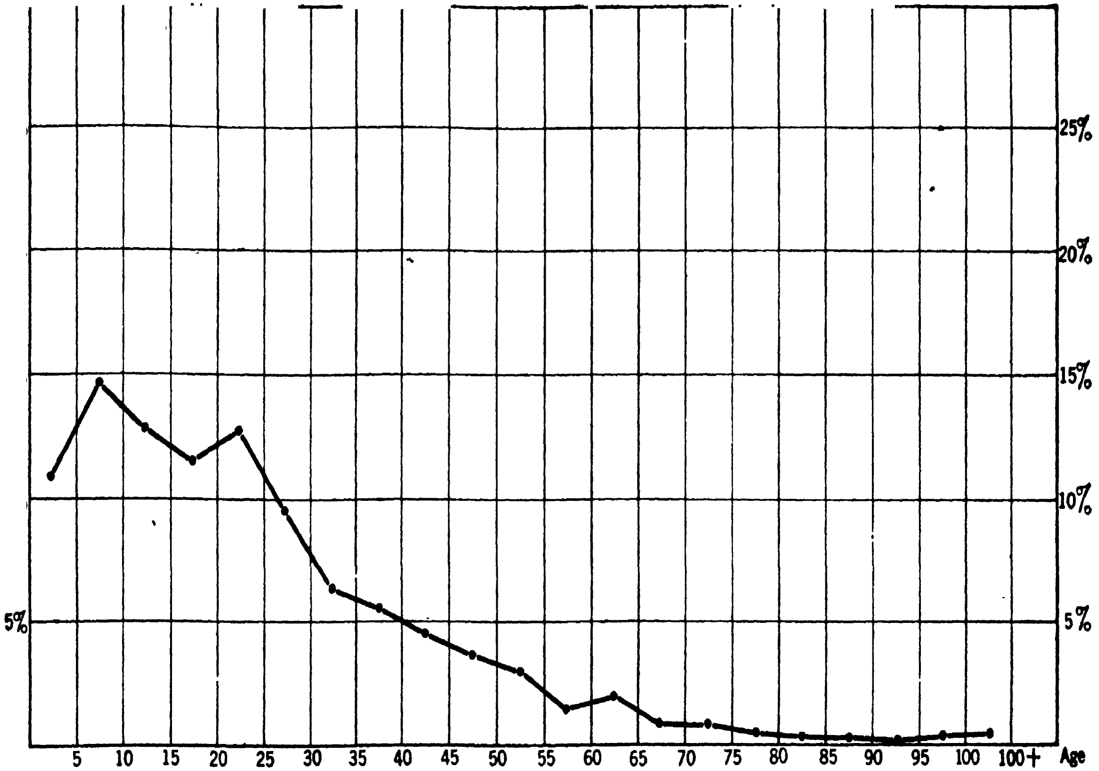


Fig. 5.—Chart Showing the Percentage of All the Malaria Found by First Blood Examination of 31,459 Persons, in Each Five-year Age-Group.

larial invasion, while others hold that they are as susceptible as the whites. The truth lies between these two extremes. Adult negroes reared in malarial regions are much less liable to paludism, as long as they remain indigenous, than are the whites. The negro race does not, however, enjoy an absolute but only a relative immunity from malaria."

A blood examination of 31,459 persons in Bolivar County showed that 16.99 per cent. of whites were infected as against 22.21 per cent. negroes. There was therefore 30.72 per cent. more malaria found in negroes than in whites. It is believed that this is the largest number of systematic blood examinations of white and colored individuals living in the same locality and under practically the same conditions in close association with each other that has ever been made. It is probable that these figures are more trustworthy and more certain to indicate the facts than is any other source of information at present available. A blood examination was made of everybody living within an area of more than 300 square miles.

(9) *Heredity: Family Predisposition.*—Malaria parasites cannot pass from the mother to the fetus and there is therefore no inherited malaria. It is a fact that the maternal side of the placenta is frequently loaded with malaria parasites. A new-born child has no malaria parasites, but is of course susceptible to infection, and if it is born in a house where the mother and perhaps other members of the family suffer from malaria, the chances of early infection are great. It is not uncommon to see babies not more than two or three months old who have become infected with malaria under these circumstances. Sometimes there seems to be a very marked family predisposition to the disease. This, however, is only apparent. The cause of the apparent predisposition is the fact that the family are all exposed to infection.

In this connection, the author wishes to emphasize, if possible, the very great importance of family transmission of malaria. If one member of a household is infected, there is a much greater chance of transmission from him to other members of the same household than to persons living in other houses. This is especially true in rural districts where residences are usually some distance apart. *Anopheles* mosquitoes have a habit of taking their blood-meals at the same house, or, at least, they show a tendency to do so. Of course, if houses are located close together, there would be less chance of an infected mosquito's returning to the same house to get another blood-meal than would be the case if the sources of supply were farther apart. This fundamental fact, underlying the malaria problem and especially the problem of malaria control, can be taken into account to great advantage.

(10) *Personal Condition: Individual Susceptibility.*—Experimental inoculation of people who have not previously had attacks of malaria indicates that all or practically all persons are susceptible to infection, and certainly in almost all cases suitable infection results in clinical symptoms of malaria. We may therefore look upon all persons as being susceptible, although naturally a greater susceptibility may be found in one individual than in another. Isolated or repeated previous attacks,

especially during childhood, result in a degree of resistance sufficient to prevent clinical symptoms in a large per cent. of cases, although perhaps not sufficient to prevent infection. It seems also that the amount of infection introduced has something to do with whether or not an individual develops clinical symptoms. Therefore, although an individual might escape the disease if bitten by only one or two infected mosquitoes, he would be apt to develop it if bitten by hundreds of infected mosquitoes. As has been seen, certain influences, such, for instance, as sudden exposure, chilling of the body, overeating, indigestible food, etc., may precipitate attacks in susceptible individuals who otherwise might not have clinical attacks. It is reasonable to suppose that individuals who possess sufficient resistance or insusceptibility to prevent their becoming infected under ordinary circumstances might become infected if the inoculation took place at times when their normal resistance was greatly reduced.

Not only is there individual variation in susceptibility to infection, but there is also great variation in susceptibility to the clinical effect of the disease. It frequently occurs that in a family or group of people who have been exposed to infection, one or more may have ordinary chills and fever, others may be malaria carriers without showing any recognized symptoms, and another one or two, perhaps infected from the same source, may develop pernicious malaria and die. For this reason, an individual infected with malaria, whether he is simply a malaria carrier without clinical symptoms or a mild case, may be the source of the worst form of malaria and death to his family and to those with whom he lives in close contact and to whom he is therefore likely to be a source of infection.

(11) *Social Conditions: Class Diseases.*—(*a*) *Cities versus Country.* —Malaria is a rural and not an urban disease. Under conditions favorable for the production of *Anopheles* it sometimes happens that they are present in cities of considerable size and may transmit malaria. In the built-up sections of cities there are usually few favorable breeding places for *Anopheles.* Cities in the tropics that are surrounded by jungles and ideal breeding and protecting ground are usually badly infected. *Anopheles* fly, under varying conditions, and may transmit malaria as far as half a mile from their breeding ground and protecting forest or jungle; but the residences nearest to such places are in greatest danger. The smaller and more compact the city or town, the more likely are malaria-transmitting mosquitoes to feed upon the inhabitants and to infect them.

In any malarious section, although there may be somewhat more malaria in the country, there are usually numerous cases among the inhabitants of the towns. Their frequent excursions into the country expose them to infection, and usually the poorly-kept town has many places favorable for the breeding of *Anopheles.* Although the towns are not as favorable for the growth of *Anopheles* as is the immediately surrounding territory, they are sufficiently favorable so that during a rainy spell or season, otherwise conducive to the growth of *Anopheles,* numbers of this insect from the surrounding country overflow into the town and produce large numbers of progeny. Malaria is, however, a rural disease to such an extent that in the majority of instances if it were eliminated from the country it would naturally disappear entirely from the towns and cities.

(*b*) *Exposure to Hardship and Cold.*—Great hardship, violent exertion and exhaustion predispose to the development of clinical symptoms in already infected individuals. A surgical operation, for instance, or childbirth, is frequently followed by symptoms in those who have not exhibited symptoms for many months, although they may have been carrying the infection about all the time. This being the case, it is reasonably certain that certain conditions increase the susceptibility to infection as well. It is the author's opinion that an even, cold temperature reduces the susceptibility to malaria infection. It is also certain that infection is not likely to take place during cold weather.

(*c*) *Natives versus Newcomers and Immigrants.*—Persons who have lived in a malarious section for a long time and have had repeated attacks of malaria, especially during childhood, are less susceptible to infection and to the development of clinical symptoms than are newcomers and immigrants, especially those who have not thus acquired more or less resistance to the disease, or those from a non-malarious locality. Persons from non-malarious countries, on coming to a malarious region, develop clinical malaria more frequently than the natives, and they also have a much more severe type of the disease. This is especially true of adults.

(*d*) *Filth, Overcrowding, Bad Ventilation, Poor Lighting.*—Filth has nothing to do with the production and development of malaria except that persons who are careless as to cleanliness are much less likely to protect themselves against malaria.

Overcrowding would tend to increase the transmission of malaria in otherwise favorable localities.

Bad ventilation has nothing to do with the development of malaria or with its transmission, except that close quarters offer favorable resting and hiding places for *Anopheles.*

Poorly lighted or dark residences offer more favorable resting places and hiding-places for *Anopheles* than do well-lighted quarters. In this way they favor the transmission of malaria. There is a rather general opinion in much of the heavily infected malaria section of the United States that sleeping in well-lighted houses or keeping bright lights burning during the night tends to prevent malaria. There is possibly a certain amount of truth in this, for *Anopheles* do not venture into well-lighted houses and rooms as they do into dark ones.

(*e*) *Occupational Diseases.*—Occupation has no influence upon the occurrence of malaria except in so far as it may influence the exposure to infection or possibly to those hardships and other factors which tend to precipitate attacks in infected persons. It is true that individuals of the laboring class usually live in poorer houses and, especially, in houses which are poorly screened, if screened at all. This fact tends to favor the transmission of malaria. Also, such individuals have not the same advantage of proper medical treatment, and therefore cannot overcome malaria infection to the same extent as those who can better afford proper medical attention.

Ignorance tends to increase the prevalence of malaria in two ways. Any person who is at all well informed knows that malaria is transmitted by mosquitoes and that it may be prevented by proper screening. The more ignorant class of people, on the other hand, do not realize and appreciate this to the same degree, and in fact do not screen their homes to the same extent, nor as effectively as do the better informed. In the light of our present knowledge as to the effectiveness of **quinin** treatment for disinfecting individuals affected with malaria, it seems that intelligent, well-informed individuals hardly deserve any sympathy if they have malaria. A man who lives in an intensely malarious section and who does not protect himself and family by properly screening his home, provided he can possibly afford to do so, shows himself to be extremely ignorant or neglectful of his own health and of that of his family.

(12) *Toxic Agents: Drugs, Dust, Fumes, Vapors, Gases, Acids, etc.*—These play no part in malaria.

(13) *Diet: Disorders of Metabolism.*—So far as any information at the author's disposal is concerned, no particular diet especially predisposes to malaria, although it would not be surprising to discover that diet does play an important part in the susceptibility to this and to many other diseases through its effect upon the natural or acquired processes of immunity. Overeating of indigestible food, such for instance as muscadines, watermelons, green fruit, etc., predisposes to the precipitation of attacks in individuals who are already infected, and in all probability also to increased susceptibility to infection in the event of inoculation.

(14) *Worry: Mental Shock.*—Great worry or mental strain tends to precipitate attacks in individuals who are already infected. Perhaps it may also render infection more likely in the event of inoculation.

(15) *Overexertion: Strain.*—Great physical strain or overexertion tends to precipitate attacks of malaria in infected individuals. An exertion approaching exhaustion is likely to precipitate attacks in malaria carriers who have perhaps escaped recognized clinical symptoms for many months.

(16) *Trauma.*—It frequently happens that following trauma involving considerable shock, malaria develops in persons who are already carrying the infection but have not active clinical symptoms. Surgical operations are frequently followed by the development of clinical symptoms of malaria in persons who have been previously infected but who show no clinical symptoms at the time. Childbirth is also frequently followed by the development of clinical malaria in infected women.

(17) *Imperfect Sewerage and Contaminated Water Supplies.*—It is not generally appreciated how great a factor imperfect water and sewerage systems are in the production of mosquitoes and thereby in

the transmission of malaria in small towns in malarial sections. This is especially true in those localities where artesian well water is used to any considerable extent.

The town of Ruleville in Sunflower County, Mississippi, which the author investigated in 1918, is an illustration of the way in which an imperfect water system may be responsible for a great deal of mosquito breeding. In this little town, not more than about half a mile square, which has a population of a thousand, at the most, eighty-nine different mosquito-breeding pools or accumulations of water due to leaking water pipes or hydrants were found. The water is supplied by flowing artesian wells and is inexpensive. There is no necessity to economize, and therefore a leaking water pipe or waste of water, unless the overflow is sufficient to produce great inconvenience to some one, does not attract attention and is not corrected. For months and years leaking pipes are allowed to leak, and it does not require a large amount of water to saturate the soil and finally form a pool. These pools are frequently more or less overgrown with grass and other vegetation and furnish ideal breeding ground for *Anopheles*. In Ruleville it was possible to prevent mosquito breeding almost entirely, simply by requiring that all leaking water pipes be repaired and that no waste water be allowed to accumulate and produce pools. There are hundreds of towns in the Mississippi Delta in almost the same condition. Most of the mosquito breeding that is going on is due to defective water pipes and sometimes also to defective sewerage and drainage. The overflow from septic tanks is frequently not properly taken care of, and although not likely to be a source of *Anopheles*, it may be a great breeding-place for other mosquitoes.

(18) *Pregnancy.*—There seems some difference of opinion as to whether pregnancy predisposes to attacks of malaria in otherwise infected individuals. Mannaberg[4] says, "Pregnancy constitutes no protection against malarial infection, notwithstanding observations to the contrary. In a gravid woman the infection often takes a severe form." Abortions occur frequently and are due in all probability largely if not entirely to the localization of malaria parasites in the uterine vessels. These may be considered the exciting cause of the abortion. The danger of abortion is greater as the pregnancy advances. The fetus is usually dead in cases of abortion and frequently has been dead for several days.

It is important to know that malaria is very likely to give rise to abortion if not treated, because of the fact that with most of the laity the idea prevails that quinin is likely to produce it. It should be known that it is the malaria which produces the abortion in most cases in which it occurs following the taking of quinin for malaria, and not the quinin itself. There is much greater danger of abortion resulting from malaria than from the taking of quinin. There is, therefore, no question as to the proper choice in cases in which malaria and pregnancy co-exist. It is even more important to give quinin in cases of malaria accompanied by pregnancy than in others, because if not controlled the malaria is very likely to cause abortion and loss of life.

TABLE 1.—RECURRENT CASES OF ESTIVO-AUTUMNAL MALARIA PROBABLY NOT DUE TO RE-INFECTION. (*Craig*)

Case No.	Initial Attack	First Recurrence	Second Recurrence	Third Recurrence	Fourth Recurrence	Fifth Recurrence
1	Oct. 12	10 days	30 days	36 days		
2	Nov. 19	12 days				
3	Feb. 27	15 days	20 days	30 days		
4	Nov. 2	18 days	30 days	30 days		
5	Mar. 30	19 days	20 days			
6	Dec. 8	19 days				
7	Jan. 24	20 days				
8	Feb. 12	20 days	60 days			
9	Dec. 24	20 days				
10	Feb. 6	20 days	20 days			
11	Feb. 6	20 days	48 days			
12	Dec. 25	21 days	33 days			
13	Mar. 1	22 days				
14	Nov. 29	22 days				
15	Nov. 14	24 days				
16	Feb. 4	24 days	20 days	38 days	30 days	
17	Oct. 30	24 days	16 days			
18	Aug. 29	24 days	26 days			
19	Mar. 17	24 days				
20	Feb. 4	25 days	16 days	20 days		
21	Dec. 30	26 days	36 days	30 days	90 days	30 days
22	Jan. 26	26 days	48 days	90 days		
23	Jan. 11	26 days	22 days			
24	Oct. 2	27 days				
25	Nov. 2	27 days				
26	Mar. 2	27 days	52 days			
27	Feb. 5	28 days	21 days	20 days	21 days	
28	Dec. 12	28 days	28 days			
29	Oct. 29	29 days	48 days	15 days		
30	Jan. 17	30 days				
31	Jan. 1	30 days	30 days			
32	Jan. 10	30 days				
33	Jan. 20	32 days				
34	Oct. 19	33 days	26 days	90 days		
35	Jan. 19	34 days	40 days			
36	Oct. 18	34 days	50 days			
37	Jan. 25	34 days	26 days	17 days		
38	Oct. 21	36 days	56 days			
39	Feb. 30	36 days	66 days			
40	Aug. 13	36 days	35 days			
41	Nov. 27	36 days				
42	Sept. 1	37 days	49 days			
43	Oct. 18	38 days				
44	Oct. 17	38 days				
45	Aug. 13	38 days				
46	Sept. 6	41 days				
47	Oct. 31	42 days	20 days			
48	Jan. 1	45 days	30 days			
49	Nov. 3	46 days	21 days			
50	Dec. 7	49 days				
51	Feb. 24	50 days	24 days	41 days		
52	Oct. 24	51 days	39 days			
53	Jan. 18	61 days	156 days			
54	June 14	64 days	66 days	14 days	20 days	20 days
55	Mar. 3	80 days	120 days	96 days		

TABLE 2.—RECURRENT CASES OF TERTIAN MALARIA PROBABLY NOT DUE TO RE-INFECTION. (*Craig*)

Case No.	Initial Attack	First Recurrence	Second Recurrence	Third Recurrence	Fourth Recurrence	Fifth Recurrence
1	Nov. 2	16 days	21 days	....	....	....
2	Aug. 4	18 days	20 days	....	....	....
3	Aug. 28	19 days	30 days	26 days	46 days	....
4	Nov. 6	20 days	24 days	....	....	....
5	Jan. 17	20 days	32 days	30 days	24 days	....
6	Nov. 23	21 days	20 days	26 days ..	....	....
7	Oct. 6	21 days	30 days	....	....	....
8	Sept. 17	21 days	22 days	27 days ..	....	....
9	Aug. 27	22 days	36 days	....	....	....
10	Feb. 12	22 days	18 days	16 days	27 days	....
11	Jan. 17	27 days	....	....	....	....
12	July 20	30 days	....	....	....	....
13	May 3	30 days	....	....	....	....
14	Nov. 1	30 days	....	....	....	....
15	Sept. 22	33 days	....	....	....	....
16	Sept. 1	37 days	....	....	....	....
17	Dec. 13	38 days	....	....	....	....
18	Sept. 22	41 days	....	....	....	....

(19) *Previous Attack.*—Whether or not an attack of malaria will be followed by relapses or subsequent attacks will depend largely upon the treatment the patient undergoes. If thorough treatment is given, so that the patient is disinfected, an attack is not followed by subsequent recurrences except in cases of re-infection. If, on the other hand, the treatment is not sufficient to disinfect the patient, there is great probability of a relapse. The frequency of malaria relapses is very much greater than it is generally supposed to be. Tables 1 and 2 are taken from Craig's "The Malarial Fevers" and represent cases of malaria in which re-infection was considered at least very improbable and which are therefore reasonably certain to be relapses. Craig says that all of them received thorough quinin treatment during the active symptoms and that most of them received prophylactic quinin once a week. It is noteworthy that, in the case of tertian malaria, those who had their first recurrence after the twenty-sixth day never had subsequent recurrences. It is possible, however, that the small number of the cases examined may cause this apparently striking difference.

In the author's investigation of malaria in Sunflower County during 1918, conclusive evidence was obtained that at least 37 per cent. of the individuals who have attacks of malaria during a given year will also have attacks during the following year, independently of re-infection.

James[5] says that in 1911 the Department of Sanitation of the Isthmian Canal Commission sent out to authorities on malaria in different parts of the world a circular letter in which information was requested as to the amount of malaria due to relapse and to other factors. Practically all the authorities referred to agreed in stating that a very large proportion of malaria, from 50 to 90 per cent., in malarious communities, is due to relapse.

An analysis of the data in the Sunflower County studies of 1918 shows that more than 50 per cent. of the attacks of malaria occurring during a given year in that locality are relapses. A fuller discussion of these observations will be found in the Osler Anniversary Volume.[6]

(20) *Chronic Alcoholism.*—Chronic alcoholism tends to increase the probability of attacks in infected individuals. Alcoholism also tends to increase the probability of the occurrence of pernicious malaria.

(21) *Association with Other Diseases.*—Malaria may be associated with any other disease. There is no disease which prevents the occurrence of malaria. On the other hand, a good many of them tend to increase the susceptibility to clinical attacks of malaria in infected persons. Anything that lowers the general vitality of the individual increases his susceptibility to attacks of malaria. Debility, chronic disease, cachexia and allied conditions, focal infections, etc., all increase the susceptibility to attacks of malaria, provided always the malaria parasites are present.

2. EXCITING CAUSE: THE MALARIA PARASITE.—A. *Morphology and Development.*—The parasites of malaria are organisms belonging to the division *Protozoa,* class *Sporozoa,* order *Hæmosporidia.* There are three varieties: *Plasmodium malariæ* (the quartan parasite), *Plasmodium vivax* (the tertian parasite), and *Plasmodium falciparum* (the estivo-autumnal parasite). There are at least two and probably more subdivisions of the estivo-autumnal parasite. Whether these are truly different parasites or whether they are simply widely differing strains of the same parasite cannot be stated definitely at the present time. A majority of students believe that there are at least two different parasites—the quotidian estivo-autumnal and the tertian estivo-autumnal. They are similar, however, in most respects and for all ordinary purposes there is no great need for differentiation.

(*a*) *The Life Cycle of Malaria Parasites in Man.*—The life cycle of malaria parasites in man is of much importance and interest. Although there are at least three distinct parasites, they all live, grow and reproduce in the body of man in very much the same way. We can therefore conveniently describe this life cycle and then take up the separate descriptions of each one of the parasites: The youngest form, the merozoite, consists of a mass of protoplasm containing a nucleus which is quite rich in chromatin. The merozoite as set free by the segmenting schizont has one flattened side and one round or oval side. It is rather cup-shaped. The nucleus is situated more or less toward the periphery. Under favorable conditions the merozoite fastens to an erythrocyte, the flat side always against the erythrocyte. On account of the clear, nonstaining vacuole which the parasite contains at this stage, it appears in stained specimens to be ring-shaped. It is frequently spoken of as a signet ring.

As time progresses the parasite grows, becoming larger and larger

PLATE I.

SCHIZONTS

GAMETES

QUARTAN MALARIA PLASMODIA

(*Plasmodium malariæ*)

(By permission of Drs. Bass and Johns, of New Orleans, and Rebman Company, of New York)

until in twelve or fifteen hours, in most cases, an examination of fresh preparations of blood shows one or more small, brownish, dancing pigment granules in the parasite. In the case of the tertian parasite and also of certain strains or divisions of the estivo-autumnal, the parasite is quite ameboid. The quartan parasite and others of the estivo-autumnal type are only slightly ameboid. In most ameboid specimens the parasite projects pseudopodia into or perhaps to the surface of the erythrocyte and presents the greatest multiplicity of figures. In living specimens, with suitable illumination, one may see the greatest activity of the protoplasm, not only in its movement through or on the erythrocyte, but also in the mass itself, as evidenced by the dancing of the pigment granules. Apparently the substance of the erythrocyte is consumed as the parasite grows, and no doubt serves as part, at least, of the latter's nutriment. The hemoglobin of the erythrocyte is broken up into globin and hematin and the latter goes to make the pigment granules.

In from twelve to twenty-four hours the nucleus becomes polymorphous and begins to divide. It was formerly thought that division of the nucleus did not take place until the full maturity of the parasite, but such is not the case, as anybody can observe by following the development of the parasite in cultures. As the development advances the pigment increases in amount, and soon after the middle of the developmental period is passed it begins to collect in a mass in some part of the parasite. Usually the tendency is for it to collect about the center, but often it is also found nearer the periphery. Formerly the pigment granules were rather widely scattered throughout the protoplasm of the parasite. Long before full maturity has been reached, especially in estivo-autumnal parasites, these pigment granules have all collected in a single compact mass, and they attract attention, in fresh specimens, to the presence of the parasite.

Although the division of the nucleus is going on all the time after the middle of the developmental period, there does not seem to be any division of the protoplasm until toward the last of the period. The developmental period varies from about thirty hours to seventy-two hours in artificial cultures. It probably varies in this same way in the tissues of man. When full maturity is reached the parasite occupies a large part of the remaining erythrocyte. Most of the erythrocyte has been consumed, leaving little more than a thin shell or capsule containing the fully developed parasite. Suitably prepared specimens at this stage show that not only has the nucleus divided into a variable number of small nuclei, but that the protoplasm has also divided so that now each small division of nucleus is accompanied by its own division of protoplasm. We have, in fact, a capsule containing a number of young malaria parasites, the result of segmentation of the original parasite. This division by segmentation without sexual influence is known as schizogony and parasites which divide and develop asexually in this way are known as schizonts. There is some difference in the use of the term, some authorities calling only the fully developed and segmented parasites schizonts, whereas others call them schizonts at any stage of their development. The author's impression is that all asexual parasites should be called schizonts.

At about this time the capsule containing the fully developed and segmented parasite ruptures, setting free its contents, consisting of the young parasites, now merozoites, the pigment granules and other material contained within the capsule. Each merozoite is capable, if conditions are favorable, of attaching itself to another erythrocyte and passing through a similar cycle of development, giving rise in turn to another crop of merozoites which may continue the process. Fortunately, most of the young parasites produced are destroyed by the protective agencies of the body. Generally they are phagocyted by the endothelial cells lining the capillaries in which the process takes place. The large mononuclear leukocytes phagocyte and destroy many of them. It is not certain what part the blood-plasma may play in their destruction. In artificial cultures the young merozoites cannot withstand the action of blood-serum for any length of time. They are very promptly affected, so that they do not take the stain in the normal way and are apparently killed. We have never been able to grow merozoites that have been exposed to the action of serum in the culture.

(*b*) *Segmentation Taking Place Especially in the Capillaries.*—The general impression is that malaria parasites live, grow, develop and reproduce in the blood stream. As a matter of fact, nothing of the sort occurs. It is true that young parasites are present in the blood stream at almost all times and also that ameboid parasites appear and reappear in the circulating blood in individuals suffering from malaria. In fact, a large part of the life cycle of the parasite is spent lodged in the capillaries of different organs and tissues, particularly in the bone marrow, spleen, etc. Estivo-autumnal parasites disappear from the peripheral circulation by the time they have reached one-fourth their full size and do not reappear at all, except inasmuch as the merozoites produced by segmentation may appear attached to other erythrocytes as young parasites. As soon as those parasites which have little ameboid motility reach such a size that they cannot adapt themselves so as to pass through the narrow places in the capillaries, they lodge and remain there for the remainder of their developmental period, which, as just stated, is about three-fourths of the entire life period. It is very probable that the merozoites that do succeed in attaching themselves to erythrocytes do so before they are dislodged from the capillaries in which they were produced.

The more ameboid parasites, as, for instance, the tertian, are capable of moving and changing their shape in such a way as to pass through the capillaries very much as leukocytes and erythrocytes do, and this is the explanation for the fact that parasites in all stages of development may be seen in the peripheral blood. It must never be thought that anything like all of the parasites in the body of an individual are present in the circulating blood. In reality, the large parasites that are seen are simply overflow, or parasites that have
through the capillaries. One

PLATE II.

SCHIZONTS

GAMETES

TERTIAN MALARIA PLASMODIA

(*Plasmodium vivax*)

(By permission of Drs. Bass and Johns, of New Orleans, and Rebman Company, of New York)

of parasites present in an infected individual by noting the number of parasites in the circulating blood.

(*c*) *The Tendency of Malaria Parasites to Reproduce by Crops.*—There is a tendency to reproduce by crops on the part of all species of malaria parasites. This tendency, however, is very much more marked in the case of the tertian and quartan than in the estivo-autumnal type. In the tertian the cropping is almost always sufficiently definite to give rise to the characteristic intermittent fever. Usually if we examine a blood specimen from a case of tertian malaria we will be able to recognize that almost all of the parasites are of approximately the same size and age, or, in instances of two different sizes and ages, one approximately twenty-four hours older than the other. As a result of this tendency to development by crops, almost all of the parasites in a given infection segment at about the same time of day. Those that have grown a little faster seem to slow down their growth as they approach maturity and those that are behind hasten and catch up. It is believed that almost all the parasites segment within a comparatively short time, perhaps only a few minutes. In cases in which there are sufficient parasites to give rise to clinical symptoms, there are countless millions of parasites present, each one of which sets free from the capsule within which it developed whatever toxic or harmful material it contains. There is a difference of opinion as to whether or not any toxin is produced, but there is certainly something that has a definite effect upon the system. Whether that something is in the nature of a toxic substance or whether it is the effect of a foreign protein, as suggested by Vaughan, or whether it is due to the effect of the pigment, as suggested by Brown, is not known.

The first effect of the segmentation of a crop of parasites of sufficient number is to cause a general relaxation of the entire vascular system, resulting in the accumulation of the blood in the large vessels, and in the organs and tissues of the body where there is least pressure upon the blood-vessels. The result of this is that very little blood passes through the surface of the body and that therefore it is not kept warm and tends to assume the temperature of the surrounding air. The patient has a chill which lasts a variable length of time, depending upon the amount of toxin produced, the length of time required to eliminate or neutralize it and perhaps upon other factors which we do not at present understand. The symptoms and the manner in which they are produced are discussed at greater length in another chapter.

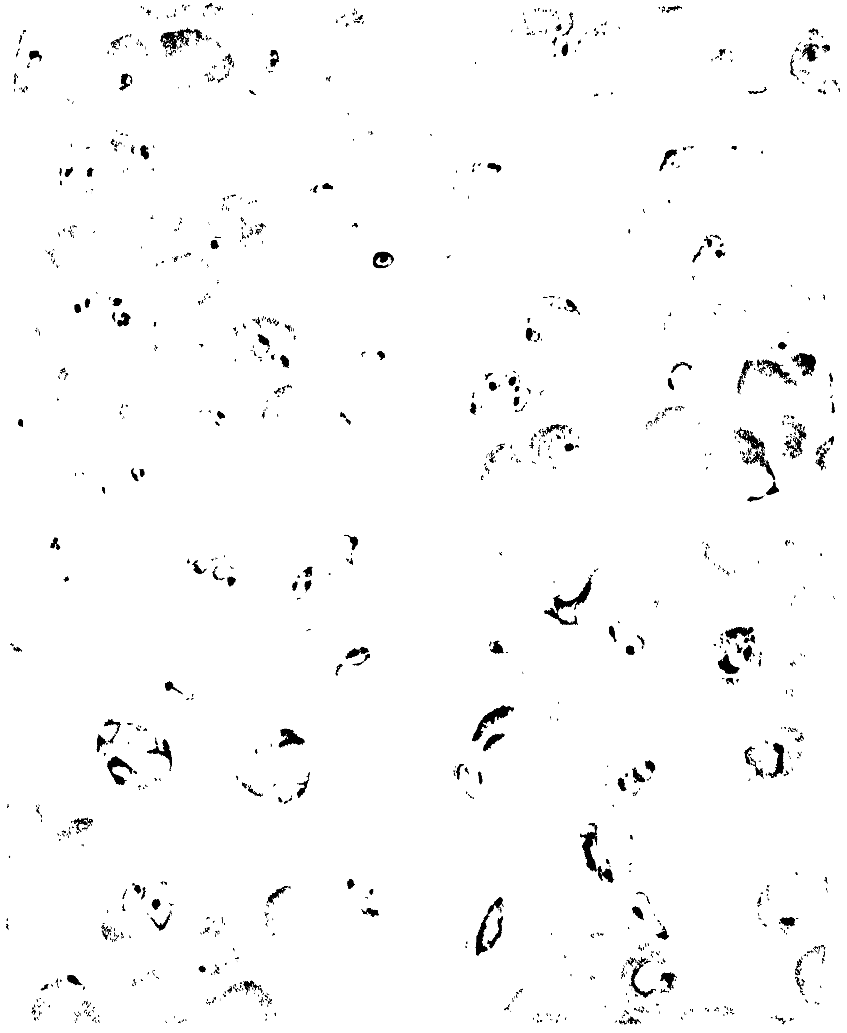
The crop of merozoites produced at the time of segmentation in a given case will mature and segment again in forty-eight hours in the instance of tertian and estivo-autumnal and in seventy-two hours in the case of quartan. If two crops of parasites are present, there is segmentation on each day, giving rise to the quotidian chill and fever; but it must be fully understood that this represents two infections and two cases of malaria in the same individual.

Asexual reproduction, such as has been described, may go on for several weeks, and if the resisting agencies of the individual are not sufficient to prevent it, the patient is finally destroyed. In most instances the destruction results from the obstruction of the capillaries of vital organs and tissues of the body, producing what is rightly called pernicious malaria. In pernicious malaria the capillaries of vital organs, such as the brain, liver, kidneys and digestive system, are obstructed with so many parasites that there is not sufficient circulation to support the tissues and the functions of the organs. The preponderance of parasites obstructing the capillaries of one organ or another gives rise to the different clinical types of pernicious malaria. For instance, "cerebral malaria" is due to the localization of large numbers of parasites in the capillaries of the brain.

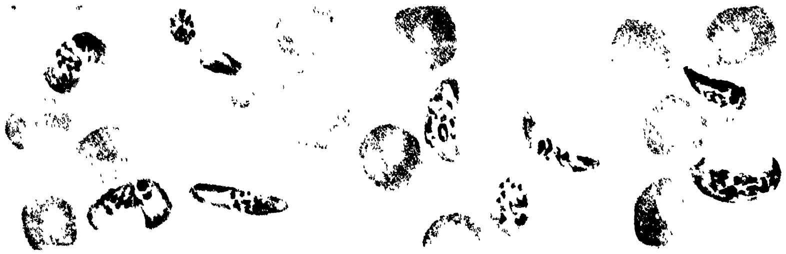
(*d*) *The Development of Sexually Differentiated Parasites.*—If an individual has had clinical malaria for ten days or two weeks, we are able, on careful examination of the blood, to recognize not only these asexual parasites, which have just been described, and which grow, develop and segment, giving rise to the clinical symptoms of malaria, but also a few or sometimes many other parasites which are different from these schizonts and which are known to be sexually differentiated. Those who are familiar with them are able to recognize and differentiate the male and female parasites. As they develop, instead of their nucleus becoming polymorphous and finally dividing, it remains single. These sexually differentiated parasites are known as macrogametocytes and microgametocytes, both commonly called gametes. Tertian and quartan gametes are sufficiently ameboid to enable them to pass through the smaller capillaries and therefore to appear and reappear in the peripheral circulation. The gametes of estivo-autumnal malaria are long, slender, and crescent-shaped, and show very little ameboid ability. Their size and shape permit them also to pass through the smaller capillaries and to appear and reappear in the peripheral circulation. The gametes of tertian and quartan malaria are round or oval and possess considerable ameboid ability, which facilitates their passage through the capillaries.

(*e*) *Parthenogenesis.*—There is considerable difference of opinion as to whether or not gametes are capable of reproduction in the body of man. It is certain that they do not reproduce sexually. There are, however, a good many students of malaria who believe that they do reproduce under special conditions by parthenogenesis. Craig has been an especially strong advocate of this view. By parthenogenesis is meant reproduction by female parasites somewhat like that which takes place in schizogony in asexual parasites, but without sexual influence. The author does not particularly favor the idea of parthenogenesis of malaria parasites: first, because parthenogenesis is not necessary to explain recurrences, more improved methods of examination having demonstrated that there are usually a few asexual parasites present for long periods after clinical symptoms have ceased; second, because, in artificial cultures in which only schizonts were present, pictures have been observed which resemble what has been considered to be parthenogenesis. The author does not feel prepared to state emphatically that partheno-

PLATE III.



VARIETIES OF SCHIZONTS FOUND IN THE PERIPHERAL CIRCULATION



GAMETES

Estivo autumnal Malaria Plasmodia

(*Plasmodium falciparum*)

(By permission of Drs. Bass and Johns, of New Orleans, and Rebman Company, of New York)

a comparatively small amount of protoplasm and a nucleus. These are known as sporozoites. This development requires a period of from about fifteen to twenty-five days in mosquitoes kept under artificial conditions. The temperature at which they are kept has a great deal to do with the rate of development. They develop very slowly at low temperatures and very much more rapidly at high temperatures.

When the period of full development has been reached, the oöcyst ruptures, setting free into the cœlom, or abdominal cavity, of the mosquito a large number of sporozoites which are carried in some way, probably by the circulatory system of the mosquito, to all parts of the insect. Some of them reach the salivary gland, which seems to be especially inviting for them to collect in. In suitable preparations the sporozoites appear to be not only in the tubes of the glands but in the gland-cells themselves. Here they remain for quite a long time unless expelled by their host in drawing blood. It has not been definitely determined just how long they can live in the glands of the mosquito host, but it is quite certain that they may pass a dormant period, perhaps as long as the life of the mosquito itself. In the infected mosquito many cysts may develop, giving rise to a very heavy infection of the glands. On the other hand, the infection of the glands may be much lighter when only one or two or a few zygotes develop.

(*h*) *The Way in Which the Mosquitoes Inject Sporozoites.*—The food of mosquitoes is not blood, as is generally supposed, but plant and fruit juices and vegetable material entirely. The male mosquitoes do not draw blood and the females do so only for purposes of reproduction. Whenever the female mosquito reaches the stage of development at which she should produce eggs, corresponding to puberty in higher animal life, there develops a desire or call for blood from which to grow eggs. Eggs will not develop in a mosquito fed only on the normal food. They will only develop after she has obtained animal protein. When this development has been reached and the desire or call is present, the mosquito starts in search of a blood-meal and will draw blood from almost any animal she finds, including man. If she draws blood from a man whose blood happens to contain malaria gametes, she becomes infected. After she obtains a blood-meal, the ova rapidly develop and sooner or later the period is reached at which she should deposit the eggs in a locality favorable to their development. She usually goes to the same breeding-ground where she herself grew and deposits the batch of eggs.

Later there is another call for blood from which to develop another batch of eggs and she goes in search of blood again, usually in the same direction and to the same locality from which she obtained blood at first. If the period between the first feeding and the next feeding has been sufficiently long for the parasites to develop and produce sporozoites and for them to reach the salivary glands, she is now capable of transferring the infection to the individual from whom she draws blood.

The blood-collecting organ, or bill, of the mosquito consists practically of a hollow needle. This needle is stuck into the skin, but in order to draw blood it is necessary that it should enter a small blood-vessel. Normally the blood-vessels are so small that it is difficult to enter them. Nature has provided this and all other blood-sucking insects with a secretion of the salivary gland which causes dilatation of the blood-vessels, or hyperemia. The mosquito first sticks her bill into the skin and then, by means of powerful muscles surrounding the salivary glands, forces some of the juice into the tissues. This causes dilatation of the vessels and usually the mosquito soon succeeds in entering a blood-vessel with her needle. Incidentally, if she has malaria sporozoites in her glands at the time, they are forced into the tissues and probably also into the blood-vessels, and the individual is infected.

It may be interesting to note that once the bill is in the blood-vessel, the mosquito is able to draw blood not by sucking, as is generally supposed, but by swallowing it as it is carried into the esophagus by capillary force.

Sporozoites introduced into the blood or into the tissues are capable of attaching themselves to erythrocytes. Perhaps they penetrate them promptly, but at any rate, they soon assume a round or oval shape, resembling merozoites produced by schizogony. They now develop in the same manner in which asexual parasites do—segment, and give rise to merozoites which continue the process of schizogony. In this manner and in this manner only are malaria parasites carried from one individual to another. The process just described applies to all species of malaria parasites.

(*i*) *Special Considerations.*—After having described the malaria parasites in general, it will now be advantageous to take up special considerations of the different species.

(1) *The Tertian Parasite.*—The merozoites of tertian parasites are about two microns in diameter. They cause rapid swelling of the host cell so that sometimes by the time the parasite is twenty-four hours old the cell is twice the diameter of normal cells. Not only does the cell enlarge but it becomes quite pale, apparently out of proportion to the enlargement. The paleness cannot be explained entirely by swelling. Specimens stained with any of the modifications of the Romanowsky stain show the presence of Schüffner's granules throughout the cell. These granules are not found in cells infected with any other malaria parasite. The parasite remains ring-shaped only a very short time, so that in practical examinations of ordinary blood preparations one seldom sees many rings. Ameboid activity begins early and is very marked. As soon as pigment is formed examination of suitable fresh blood preparations shows that it is very actively motile. It is also strikingly fine compared with the pigment produced in either quartan or estivo-autumnal parasites. The full-grown parasite is as large as, and sometimes larger than, the normal erythrocyte. All stages of the development of the parasite may be seen in the peripheral circulation, but there are only a few rosettes and parasites present as compared with the total number present in the organs and tissues in which the development is going on most extensively. The gametes are round or oval and their pigment is generally distributed throughout the protoplasm of the parasite.

(2) *The Quartan Parasite.*—The merozoites of quartan parasites are perhaps slightly smaller than those of the tertian type and they remain ring-shaped considerably longer. Usually a good many of them develop in from twenty-four to thirty-six hours in the form of bands across the erythrocyte, instead of showing the usual irregular shapes. In fact, the quartan never displays anything like the great irregularity of shape that is shown by the tertian. As the parasite develops the erythrocyte shrinks and its color intensifies. Pigment appears in from twenty-four to thirty hours and is coarser than in the tertian. It is also very much less active than in the tertian. The parasite matures in seventy-two hours and divides into not more than eight segments. All stages of the parasite appear in the peripheral circulation, but they become less numerous as they grow older. However, rosettes are frequently found in the peripheral blood. The gametes are round or oval and usually not numerous.

(3) *The Estivo-autumnal Parasite.*—The youngest merozoites in most cases of estivo-autumnal parasites are very much smaller than those of tertian or quartan. They consist of a chromatin granule and a very small ring. Sometimes there are two chromatin granules. These rings are frequently so small they are overlooked, especially by those who are not well trained and have not good staining technic. Only these small ring forms and perhaps gametes are seen in the peripheral circulation. These parasites, as they grow in artificial cultures, never reach more than about half the diameter of erythrocytes. In artificial cultures they reach full maturity in from thirty-six to forty-eight hours, and they produce apparently only about sixteen segments. These parasites have extremely little ameboid activity, which is believed to explain their disappearance from the circulation while they are small. Preparations made from half-grown or older parasites in artificial cultures, by placing a drop of the material containing them on a slide, covering it with a cover glass and then examining it under the microscope while pressing upon the cover glass, show that they are more resistant and unyielding to pressure than any of the other parasites. One gains the impression that they would not yield and mold their shape in order to pass through narrow places in the capillaries. The gametes are crescent-shaped and are to be found in the peripheral circulation.

In other specimens of estivo-autumnal parasites the merozoites are as large as those of tertian, and frequently the ring of protoplasm is considerably thicker and heavier. The definite signet ring is not present to the same extent as it is in the first form of the estivo-autumnal type. A tendency to ameboid changes is shown, but usually the parasites disappear from the circulation before this is very marked. They spend from eight to twelve hours of their forty-eight hour life period in the peripheral circulation, and the balance of the time they are lodged in the capillaries of different organs and tissues. In artificial cultures parasites do not show a great deal of ameboid change, and they finally develop to almost the diameter of the host cell. They often produce twenty-four or more merozoites in artificial cultures. This is the form which is generally called malignant tertian, the other one just described being commonly called quotidian. In artificial cultures the pigment is coarse and soon collects in a mass in some part of the parasite. The gametes are crescent-shaped and usually show very little of the remaining erythrocyte from which they developed.

The differentiation of the different varieties of malaria parasites will be aided by reference to the colored plates (Plates I, II and III) and to Table 3, taken from Bass and Johns' Laboratory Diagnosis:

TABLE 3.—DIFFERENTIATION OF MALARIA PARASITES

	Estivo-autumnal	Tertian	Quartan
Schizonts in the peripheral blood.	Rings only.	All sizes.	All sizes.
Shape of gametocytes.	Crescentic and oval.	Round or oval.	Round or oval.
Shape of outline of schizonts in peripheral blood.	Rings. May have two chromatin granules.	Irregular after ring stage is passed.	Regular after ring shape is passed.
Influence upon color of erythrocyte.	Not changed.	Faded, pale.	Darker. Normal red color intensified.
Influence upon size of erythrocyte.	Not changed.	Enlarged.	Reduced.
Pigment in schizonts and gametocytes.	Medium to coarse.	Very fine.	Coarse.
Schüffner's granules.*		Often present.	Not present.
Number of segments in rosette.		32.	8.
Period of asexual development.		48 hours.	72 hours.

*Red-staining granules in the erythrocyte containing the parasite.

B. *The Distribution of Malaria Parasites in the Body.*—It is generally supposed that malaria parasites are distributed in the circulating blood. It is true that there are some parasites present in the blood of almost all individuals who are infected but, as a matter of fact, these are either overflow parasites or those which have escaped from the capillaries temporarily as a result of ameboid activity or because of their small size or special form, as, for instance, in the case of the estivo-autumnal gamete. Probably the bone-marrow contains more malaria parasites than any other part of the body, in ordinary cases; the spleen comes next, the liver perhaps next and then come such organs as the brain, gastrointestinal canal, hematopoietic glands, etc. In pernicious malaria the number of parasites present in vital organs and tissues is frequently enormous. In many such cases even the capillaries of the skin contain large numbers. The pigment held in the capillaries of the skin is sometimes sufficient to give a pigmented or brownish yellow appearance.

C. *The Cultivation of Malaria Plasmodia.*—The first successful cultivation of malaria plasmodia *in vitro* was announced by Bass[7] in 1911. The technic was not given and, as a matter of fact, only partial success had been attained. In 1912 Bass and Johns[8] published the technic, and in September, 1912, exhibited cultures of plasmodia at the International Congress of Hygiene and Demography in Washington. These were observed by hundreds of scientists from different parts of the world and recognized by all familiar with malaria plasmodia to be genuine and to represent every stage of reproduction of the parasite by schizogony. A still more complete description of the technic, in which every detail was covered, was published by Bass[9] in 1914.

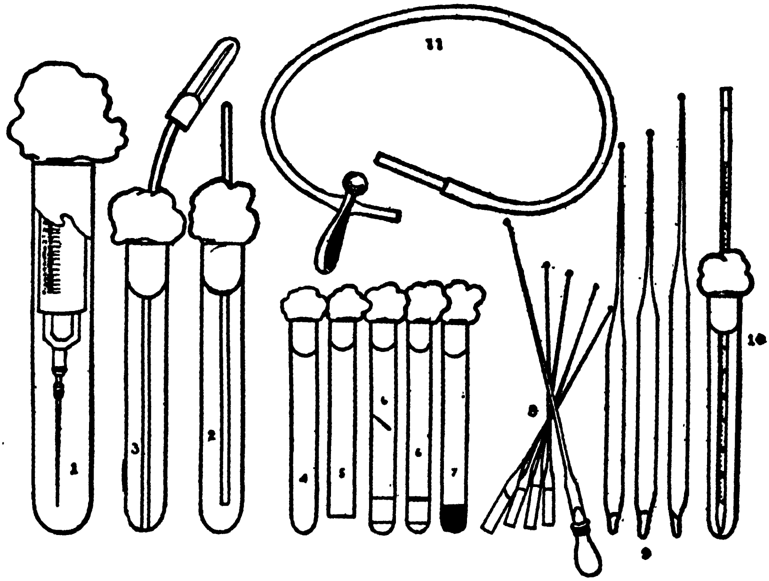


FIG. 6.—APPARATUS USED IN CULTIVATION OF MALARIA PARASITES. (Bass, American Journal of Tropical Diseases.)

Since the author's first publication of the technic, malaria plasmodia have been cultivated by different workers in almost every civilized country. They have been grown only in human blood. Success depends upon the presence of a suitable quantity of dextrose in the culture. So far as the author is informed, no successful cultivation has been accomplished without the use of the dextrose.

The following is the original *technic*, taken from the *American Journal of Tropical Diseases and Preventive Medicine* (1914, i, No. 8, 546).

"*Apparatus and Materials Required.*—One generation of parasites may be grown with very simple technic, but they are destroyed soon after segmentation, and often just before, by the leukocytes in the blood from the patient. The apparatus needed for the cultivation of one generation only of parasites are the following:

"1. Syringe and needle. An all-glass syringe, capacity 20 c.c. (or

10 c.c.), graduated, is convenient for this purpose. Syringes with rubber, leather or cotton plungers, washers, connections, etc., are not serviceable because they cannot be easily cleaned after being used, and when they are sterilized they give off substances which are harmful to malarial plasmodia. A coarse needle is necessary because strong force or strong suction so alters the cells (or parasites) that the parasites die in a short time. Such a needle is also desirable to avoid leaking and bubbling of air into the syringe and to facilitate taking blood into it and expelling it from the syringe.

"2. Defibrinating tube. Tubes 2½ cm. in diameter and of whatever length will be accommodated by the centrifuge (if a centrifuge is to be used) are appropriate. This tube is plugged with a cotton plug having a plain glass rod (0.5 cm. diameter) running through it and extending to the bottom. A glass tube may be substituted for the glass rod, in which case the outer end is connected to a needle by means of a short rubber tube (Fig. 1, 3). More recently this rubber connection has been dispensed with and the needle (barrel without any shoulder) is welded into the tubing. Platino-iridium needles are necessary for this purpose. Blood is collected directly into the defibrinating tube by sticking the needle into a distended vein.

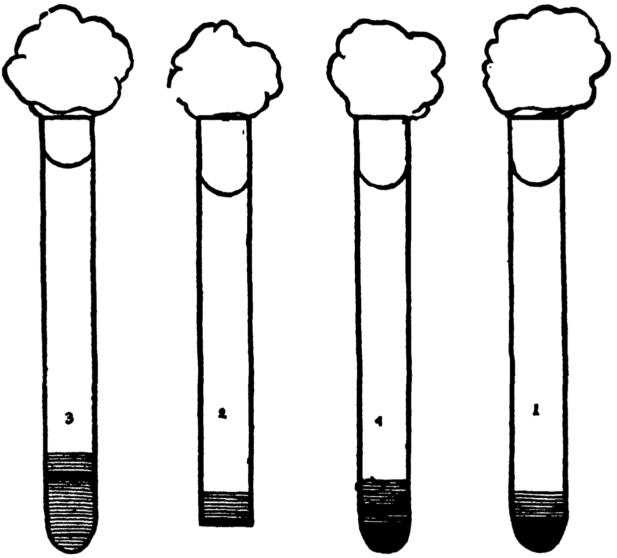


FIG. 7.—DIFFERENT FORMS OF MALERIA CULTURES. (Bass, American Journal of Tropical Diseases.)

"3. Culture tubes not less than 1.25 cm. in diameter by 12.5 cm. deep.

"4. Graduated pipet, 1 c.c. graduated in hundredths.

"5. Dextrose (Merck's) 50 per cent. solution in water. This should be sterilized at 100° C. on three consecutive days.

"6. Capillary pipets. Glass tubing 0.5 to 0.6 cm. in diameter is the proper size from which to make these pipets. The capillary should be rather coarse since fine capillaries are destructive to malarial plasmodia. The large end of these pipets should be plugged with cotton before sterilizing.

"7. Rubber bulb. This should be of the best quality and fit the pipets well. The delicate uses to which the pipets are placed require perfectly fitting bulbs.

"8. Incubator regulated to a temperature of 40° C. It is possible to use an incubator running as low as 38° C., and in fact, often the parasites grow fairly well at 37° C.

"The following apparatus will be required if more than one generation of parasites is to be grown, or if it is desired to avoid the dead parasites which are present in the deeper layers of cultures containing a thick column of cells.

"9. Centrifuge, speed 800 to 2000 r. p. m. Higher speed centrifuges are likely to be destructive to the parasites or at least to cause such changes in the cells as to disfavor their growth.

"10. Culture tubes 1.25 cm. by 12.5 cm., with flat bottom or with disk of pure white filter paper supported 1.25 cm. or more from the bottom of the tube by a piece of glass tubing. The latter should be cut straight across and should fit the culture tube fairly closely.

"11. Plain pipets, capacity 5 to 20 c.c. These pipets should be plugged with cotton before sterilizing and the small end (large capillary) should remain hermetically sealed until it is to be used. They are not used a second time.

"12. Rubber tube 50 cm. long, mouth piece and pinch cock. This tube should be of proper size to fit the neck of the large pipets just described.

"The syringes, tubes and pipets must be sterilized in the dry sterilizer. A few drops of water in a tube in which blood containing plasmodia is placed will usually cause the death of the parasites. The dry sterilization must not be carried to the extent of scorching the cotton plugs, for the smoke that condenses on the inner surfaces of the tubes is sufficient to kill all the parasites in a culture.

"*Technic for Cultivating One Generation Only of Parasites.*—Blood is collected from the patient's vein at the bend of the elbow. If drawn with the syringe it is expelled directly into the defibrinating tube. The latter should be tilted to one side and care should be taken to avoid unnecessary exposure of the blood to the air. In either case, 1/10 c.c. of the 50 per cent. solution of dextrose for each 10 cubic centimeters of blood to be taken is placed in the defibrinating tube before the blood is drawn. Defibrination is effected by gently stirring or whipping with the rod or tube which extends through the cotton plug. The whipping in of air, causing bubbles, must be avoided. The plug and rod may now be replaced by a plug from another tube of the same size.

"This defibrinated dextrose blood containing malarial plasmodia may be transferred to other tubes or incubated in the original tube. In any event the column of blood must be 2.5 to 5 cm. deep. This gives a column of serum 1.25 to 2.5 cm. deep above the cells and parasites when the latter have settled. Supernatant serum more than 2.5 cm. deep has no advantage. When this is less than 1.25 cm. deep the parasites often die before segmentation occurs. We have occasionally seen perfect segmentation, however, under 0.6 cm. of serum.

"The parasites live and develop at the top of the column of precipitated cells in a layer varying in thickness from 0.05 to 0.1 cm. All parasites beneath this layer die in from two to twenty hours; the time depends upon factors which have not been determined. Some grow considerably before they die and we have occasionally seen small ring forms attain over half the full adult size in the deep part of the cell mass. When parasites die in these deep cells the central clear space in the small ring closes, or if the parasite is older the irregular projections, pseudopodia, are withdrawn. If pigment is present it loses its motility. The protoplasm gradually shrinks, losing its staining reaction, and finally only the nuclear chromatin granule remains. This also stains poorly. In the instance of very small parasites often the red blood-cell shows little or no evidence of the previous presence of the parasite. This suggests the possibility that the young parasite had not yet entered the cell substance.

"The parasites in the thin layer at the top of the column of cells develop and may be examined at any time by drawing a small quantity of cells from this layer by means of a capillary pipette. Some considerable practice is required in order to do this without drawing cells and dead parasites from just beneath this layer. The pipet may be passed through a flame to sterilize it on the outside, but it must be allowed to cool thoroughly before it is used, since, in our experience, a temperature of 45° to 50° C. kills the parasites in a very short time.

"Such a temperature also alters the red blood-cells in some way so that they are rendered permeable to the surrounding serum, and this effect is destructive to the parasites. Great care must be taken in handling tubes containing cultures to keep them in an upright position. Tilting to the side results in burying and killing the living parasites in the thin layer at the top of the column of cells. With sufficient care a sample may be removed from the culture and the tube be returned to the incubator without killing the parasites. This may sometimes be repeated several times.

"*Technic for Cultivating More Than One Generation of Parasites.*—If more than one generation of plasmodia is to be cultivated, it is necessary to remove the leukocytes at the time the culture is made in order to avoid destruction of the parasites by them at the time of segmentation. The infected blood from the patient is centrifugalized sufficiently to force the leukocytes to the surface of the cells. The length of time necessary to centrifugalize varies with the speed, length of arm, etc., of the particular centrifuge used and should be determined by experiment. Unnecessary centrifugalization should be avoided.

"The supernatant serum is drawn off and put in culture tubes. The column of serum in each should be 1.25 to 2.5 cm. deep. Cells and plasmodia are carefully drawn from about the middle of the centrifugalized cells and planted at the bottom of the serum in the culture tubes. Flat-bottom tubes are an advantage. 1/10 to 2/10 c.c. of cells in a half-inch tube make the thickest layer in which it is possible to get a homogeneous growth of parasites.

"We have been able to secure growth of all the parasites in about twice this quantity of cells in a 1.25 cm. tube by employing tubes with a paper shelf suspended in them. They are filled with serum to at least 1.25 cm. above the level of the support for the paper disk. The disk is then carefully tucked in place, after which the cells are placed on it.

"We have obtained even more satisfactory results with tubes filled 1.25 cm. deep, or more, with freshly prepared human plasma. These are conveniently prepared by placing 1.25 to 2.5 cm. of blood, immediately after it is drawn, in culture tubes and centrifugalizing to throw the cells to the bottom before coagulation takes place. By continuing centrifugalization until after coagulation occurs, a flatter surface is secured for the plasma than if it is discontinued before this time. In such plasma bottom tubes 1.25 cm. of fresh dextrose serum is placed and then cells and parasites from the centrifugalized and defibrinated dextrose blood are carefully distributed over the surface of the plasma. We have sometimes obtained in these tubes a layer of live parasites approximately 0.25 cm. thick.

"Parasites in such leukocyte-free cultures develop, segment, and most of the merozoites enter new red blood-cells. These young parasites develop in the same manner as the first generation and sometimes reach the stage of segmentation. In fact, we have in one instance observed the development of three successive generations in such a culture. More often, however, the parasites begin to die out after the first segmentation and especially after the second. We have not been able to determine exactly the cause of this. In order to perpetuate the culture it is necessary to transfer a portion of the cells and parasites to a recently prepared tube containing fresh cells and serum. It is convenient to place the fresh serum in the culture tube and to take up in a large capillary pipet a portion of the cells and parasites of the culture and then about five times the amount of fresh cells. These are mixed in the pipet (avoid air) and then carefully spread on the surface of the plasma, paper shelf, or bottom of the tube, according to the particular kind of culture tube used. The transplantation should be done within four or five hours of the time of maximum segmentation and therefore approximately every forty-eight hours for tertian and estivo-autumnal parasites.

"It often occurs that with each successive transplant fewer parasites survive than in the previous one, and finally the culture is lost. In fact, there is little or no increase in the number of parasites in the body of man in most instances. Actually not more than one merozoite out of every fifteen to thirty survives. With the most exact technic we have secured a fifth generation containing many more parasites than the first, and there is good reason to believe that with sufficiently exact manipulations it will be possible to continue the cultures indefinitely."

The only essential change which has been made in the requirements given above are that further experience has shown that the plasmodia grow as well at 37° C. as at higher temperatures, except that possibly they grow a little more rapidly at higher temperatures, and that it is not necessary to remove the leukocytes by centrifugalization, in order to grow more than one generation.

D. *The Distribution of Malaria Parasites Outside of the Body.*—There is only one place in the world in which malaria parasites live in nature outside of the body of man and that is in certain favorable species of mosquitoes.

E. *Modes of Conveyance.*—Many investigators have succeeded in transmitting malaria by taking the blood from an individual who has malaria and injecting it into another individual. Successful inoculations have been made both by the intravenous and the subcutaneous routes.

Hereditary transmission does not take place. There have been a few instances in which malaria has been reported in very young babies, but in few if any of them could the question of postnatal infection be ruled out. The majority of observers at the present time agree that prenatal infection does not take place. When we recall the structure and arrangement of the barriers that it would be necessary for the parasites to pass, it does not seem at all reasonable that infection could take place in this way.

(*a*) *Malaria Carriers as a Source of Infection.*—The term "malaria carrier" is usually applied to persons who have malaria parasites in their blood but who do not show active clinical symptoms. Of course a person with clinical symptoms is also a carrier of malaria and likely to be a source of infection. Persons who have latent malaria and who perhaps have never shown any recognized symptoms may also be sources of infection.

The importance of malaria carriers in the transmission of malaria and in its control has not been, as a rule, fully appreciated. It is surprising, in a locality where malaria prevails to any considerable extent, to note how many people who have not had recognized clinical symptoms of malaria will be found upon blood examination to have malaria parasites. In our Bolivar County experience, which is perhaps the most extensive investigation along this line that has ever been made, out of 18,782 persons who claimed not to have had attacks of malaria or evidences of attacks during the previous twelve months, 15.93 per cent. were found, upon the first examination made of their blood, to have malaria parasites. Out of the total 31,459 persons in an area of 325 square miles in Bolivar County whose blood was examined, 21.18 per cent. were found, upon first examination, to have malaria parasites. Not more than 10 per cent. of these were actually sick of malaria at the time. It is found, therefore, that in this locality, which is believed to be representative of the malaria section of the Mississippi Delta, 21.18 per cent. of the entire population are potential malaria carriers. In fact, it is very certain that repeated examinations would have revealed considerably more infected persons and would have considerably raised the percentage of the population found to be malaria carriers.

Not all carriers have gametes in their blood at all times, and therefore not all are sources of infection to mosquitoes at any given time. They are, however, potential sources of infection and must be considered as such. If a man has one malaria parasite in his blood he may later have gametes in sufficient numbers to infect mosquitoes.

Improper treatment is largely responsible for the large number of carriers to be found in any malarious locality. Small doses of quinin not only do not disinfect the infected individual but they tend to increase the production of gametes. The use of chill tonics and drugs containing small quantities of quinin is very extensive in malarious regions. These seldom disinfect those who take them, but transform them from persons sick of malaria to unrecognized malaria carriers, and in all probability actually increase the amount of transmission of malaria which takes place.

The importance of disinfecting malaria carriers and thereby reducing transmission is the basis of one method of malaria control. There is a difference of opinion as to the probable value of this method, but in the author's judgment it is by far the most promising method at the present time. It is true that it should always be combined with such mosquito control as is practical, but up to the present time extensive malaria control by control of mosquitoes has not been accomplished except at a cost which would prohibit its application in extensive areas.

(*b*) *The Dissemination of Malaria by Mosquitoes.*—Malaria is carried from one individual to another by mosquitoes and in this way only. If there were no mosquitoes there would be no transmission of malaria. Not all species of mosquitoes are capable of serving as hosts for malaria parasites. All of the malaria transmitters so far identified belong to the sub-family Anophelinæ. Deaderick and Thompson [10] give the following list of Anophelinæ which have been determined with more or less certainty to be malaria carriers:

Anopheles annulipes.
Anopheles bifurcatus.
Anopheles cohæsa.
Anopheles crucians.
Anopheles farauti.
Anopheles formosænsis.
Anopheles maculipennis.
Anopheles martini.
Anopheles pseudopunctipennis.
Anopheles pursati.
Anopheles quadrimaculatus.
Anopheles tarsimaculata.
Anopheles vincenti.
Cellia albimanus.
Cellia argyrotarsus.
Cellia pharoensis.
Cycloleppteron grabhamii.
Myzomyia christophersi.
Myzomyia culicifacies.
Myzomyia funesta.
Myzomyia hispaniola.
Myzomyia ludlowii.

Myzomyia lutzii.
Myzomyia picta.
Myzomyia rosii.
Myzomyia turkhudi.
Myzorhynchus barbirostris.
Myzorhynchus coustani.
Myzorhynchus fuliginosus.
Myzorhynchus paludis.
Myzorhynchus sinensis.
Myzorhynchus umbrosus.
Myzorhynchus ziemanni.
Nyssorhynchus annulipes.
Nyssorhynchus jamesii.
Nyssorhynchus maculatus.
Nyssorhynchus maculipalpis.
Nyssorhynchus stephensii.
Nyssorhynchus theobaldi.
Nyssorhynchus willmori.
Pyretophorus chaudoyei.
Pyretophorus costalis.
Pyretophorus jeyporensis.
Pyretophorus superpictus.

Of the mosquitoes that may serve as hosts for malaria parasites, not all are equally efficient. Not only is this true, but the habits of some of those that are easily infected under experimental conditions are such that they are not likely to be a considerable source of transmission. Some of the wilder species, although perhaps more easily infected, are not as likely to be a means of transmission as other species not so easily infected but more domestic and more likely to feed upon human beings.

(1) *Breeding-places.*—Different species of *Anopheles* have quite different breeding habits, but most of them require fairly clean water. They also require more or less protection by vegetation, such as grass, weeds, brush and trees. Deaderick and Thompson say:

"Ground water appearing at the surface is especially suitable. Pools of at least some degree of permanence are preferable to those which might dry before the aquatic stage of the insect is completed. Natural accumulations of water more often contain *Anopheles* larvæ than do artificial collections. Pools, ponds, swamps, inlets of lakes, and of small, slowly flowing streams, ditches along roadsides, canals, borrow pits along railroads and levees, and rice fields are common breeding-places. Water contained in the tracks of animals may harbor larvæ.

"When water is scarce, as during the dry season, anopheline larvæ may be found in tubs, barrels, buckets, bottles, cisterns, mollusc and cocoanut shells, in water retained by the leaves and stalks of tropic plants, or even within vases in dwellings, although these locations are to be regarded as places of necessity and not of choice."

The eggs of *Anopheles* are deposited singly on the surface of the water or at the edge of some floating trash or débris. They vary in the length of time required to hatch, depending upon the temperature and perhaps upon other influences, but they may hatch in from two to four days under favorable conditions.

(2) *Identification of Anopheles Larvæ.*—It is not considered within the scope of this section to enter extensively into the description and identification of *Anopheles* in their different stages. It will be sufficient to say that *Anopheles* larvæ may be recognized for all practical purposes by their resting position in water. They remain parallel to the surface of the water, whereas the larvæ of all other species of mosquitoes rest at a considerable angle to the surface of the water. The

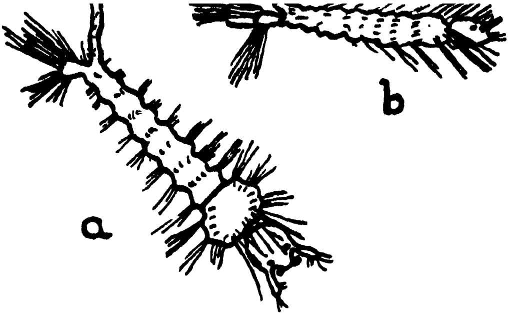


FIG. 8.—RESTING POSITIONS OF LARVÆ.
a, Culex; b, Anopheles.

larval stage lasts from twelve to fourteen days under favorable climatic conditions. In colder climates and during the cold season the larval stage may last many weeks. It has been demonstrated by Griffitts and others that *Anopheles* can pass the winter in the larval stage.[11] This, no doubt, is an important source of the first mosquitoes following the cold season. Whether many adults pass the winter is open to question. It is quite certain that a very small proportion of those alive at the beginning of the winter survive.

The duration of the pupal stage may be from about two to four days under favorable conditions. The pupæ are also quite resistant to cold. From the pupa the full-grown imago emerges and after remaining for a very short time flies away.

(3) *Identification of Adult Anopheles.*—For all practical purposes *Anopheles* may be differentiated from all other species of mosquitoes by their position when resting on a wall. The proboscis, head, thorax and abdomen are in the same line and form quite an angle with the surface upon which the insect rests. In some species almost a right angle is formed. This is in contrast to all other species. The chief malaria carriers of the United States are *Anopheles quadrimaculatus, Anopheles maculipennis* and *Anopheles crucians.* King [12] has shown that *Anopheles punctipennis* is also a host of malaria parasites.

(4) *Flight Habits of Anopheles.*—LePrince has probably made the most extensive investigations of the flight habits of the malaria-bearing mosquitoes. Experiments were conducted in Panama [13] in which *Anopheles* were marked by spraying them with a solution of eosin and then liberating them. Collections were made during the following several days and the mosquitoes collected were examined for the presence of the dye. Forty stained specimens were recovered at a distance varying from 1200 to 6250 feet from the liberation station. Five specimens were captured at the greater distance.

LePrince and Griffitts [14] made numerous investigations of the flight habits of *Anopheles quadrimaculatus* in South Carolina, employing the same method of identification that was followed in the Panama studies. These observations show that under certain conditions at least, *Anopheles* *quadrimaculatus* will fly as far as one mile from the point of liberation. In one observation where the production at the breeding-place was considerably less, the greatest distance over which flight was found to have taken place was approximately half a mile. In one test the marked specimens flew a distance of 3090 feet, 800 feet of which was over a river, in returning to the cabin in which they were first captured.

It is noteworthy that out of 270 *Anopheles quadrimaculatus* that were liberated at a distance of 3090 feet from the place where they were captured, two of them were recaptured in the same cabin within seventy-two hours after their liberation. This not only has significance as to the distance over which mosquitoes fly, but also emphasizes the idea of their tendency to return to the house from which they came. The author considers this an extremely important feature of malaria transmission that has perhaps been somewhat overlooked. Not only do mosquitoes tend to return to the same breeding-ground where they were bred, after securing a blood-meal, but there is also a tendency for them to return to the same feeding-ground after ova-position. For this reason, especially in rural communities, a malaria carrier in a given house is much more likely to be a source of infection to persons living in the same house than he is to others living in the community.

The distance over which *Anopheles* may fly under exceptional circumstances is not as important as the distance over which they actually fly under ordinary conditions in sufficient numbers to be likely to transmit malaria. Generally they do not fly over clear ground for as long distances as they do over ground where they are protected more or less by a growth of trees or rank vegetation. Being swamp or jungle species most of them do not venture great distances away from such protection from their natural enemies as is afforded by a dense growth of vegetation. *Anopheles* will follow a hedge row or a lead of trees for much longer distances than they will fly over clear ground. In the rural farming section, crops, such as corn and cotton, frequently offer favorable protection and leads for mosquitoes to reach residences situated so far from their breeding-ground that they would not reach them otherwise.

(5) *Length of Life of Mosquitoes.*—No doubt the longevity of different species of mosquitoes varies greatly and there is also no doubt that there is a great variation in the length of time mosquitoes of the same species live under variable conditions. Many species are known to pass the winter in either a hibernating or an inactive condition. The manner in which the active processes are minimized and the length of life greatly prolonged by special influences is indicated by an observation of Mitzmain [15] in which it was found that gravid females did not deposit eggs as long as they were kept at temperatures of from 4.5° to 12.5° C. In another experiment some eggs were laid at temperatures ranging between 13.5° C. and 16.5° C. At warmer temperatures the life processes are much more active and no doubt the life of the insect is much shorter. When mosquitoes are kept under artificial conditions in the laboratory, the mortality is very high. A large part of them live only a few days. One cannot conclude, however, from this that the duration of life of

Anopheles in nature is so short. It is a fact, however, that whenever mosquito-breeding is stopped in a locality where the insects are abundant, it takes only a week or two for a marked reduction to be noticeable. The average length of life of *Anopheles* must therefore vary greatly from about two or three weeks under some conditions up to at least three or four months under winter conditions. It must be understood, however, that of the large number alive at the beginning of the winter, only a very small proportion survive to the next warm season.

F. *Types of Infection.*—In simple tertian infection there may be one crop of parasites segmenting on one day and another crop segmenting on the alternate day, giving rise to quotidian fever. This is properly called double tertian infection. The most frequent type of infection, however, is single tertian in which there is only one crop of parasites, giving rise to tertian fever.

In quartan malaria there may be one, two or three crops of parasites, giving rise to quartan fever, or to quotidian on two days followed by an intermission of one day, or there may be three crops of parasites, giving rise to quotidian fever. The tendency to reproduce by crops is not so marked in the estivo-autumnal type; in heavy infection, especially, there are sufficient parasites reproducing at all times to give rise to continued fever without intermission.

In addition to these various types of pure infection, there may be mixed infections of two or three different species. It happens very frequently in localities where two species of malaria parasites are prevalent that an individual may be infected with both. It often occurs that an individual may have tertian infection during the spring and early summer and estivo-autumnal in the fall and winter. It is not common, but occasionally happens that gametes of both may be found simultaneously in the blood of an individual. One may sometimes find a few crescents in the blood of cases where all the schizonts found are tertian. Usually in cases of mixed infection one parasitic form predominates and determines the clinical picture.

Symptomatology.—CLINICAL HISTORY.—*Period of Incubation: Symptoms of Incubation Period.*—The period of incubation is necessarily influenced very greatly by the number of sporozoites introduced. For instance, the length of time required for sufficient multiplication to give rise to clinical symptoms would be very much longer where the individual had been bitten by only one infected mosquito than in another instance in which he had been bitten by many, each one introducing a number of sporozoites. It is conceivable that clinical symptoms might possibly develop after forty-eight or seventy-two hours, according to the species of malaria parasite, provided an enormous number of infected mosquitoes fed upon the individual. Barber [16] reported two cases in which the first rise of temperature occurred from fourteen to seventeen days after experimental inoculation by infected mosquitoes. These were *Anopheles rossi* infected with estivo-autumnal parasites. Mitzmain,[17] experimenting with *Anopheles punctipennis* infected with tertian parasites, allowed from one to four mosquitoes to bite each of seventeen different persons. The incubation period in the fourteen who developed malaria is shown in his table, reproduced below (Table 4).

TABLE 4.—LENGTH OF TIME EACH PERSON WAS BITTEN AND INCUBATION PERIOD RESULTING. (*Mitzmain*)

Date When Bitten	Volunteer	Infected *Anopheles punctipennis* Applied				Incubation Period (Days)
		No. 18	No. 23	No. 24	No. 25	
1916 Feb. 17	H. E. H.	1 minute	45 seconds	45 seconds	40 seconds	15
“ 18	Dr. H. A. T.	....	Complete	Complete	....	14
“ 21	Dr. R. C. D.	....	....	40 seconds	1 minute	13
“ 21	Dr. T. H. D. G.	....	....	30 seconds	40 seconds	14
“ 21	F. M. H.	....	....	1 minute	45 seconds	14
“ 21	R. E. T.	....	....	30 seconds	80 seconds	15
“ 22	Dr. R. T. O'N	....	....	1 minute	....	15
“ 23	H. T.	....	40 seconds	1 minute	....	13
“ 23	Dr. S. L. C.	....	40 seconds	30 seconds	....	13
“ 26	F. W.	....	50 seconds	....	....	16
“ 26	F. A.	....	1 minute	1 minute	....	14
“ 28	C. B.	....	Complete	Complete	....	13
Mar. 1	T. A. R.	....	35 seconds	....	....	19
“ 1	G. O.	....	1 minute	....	....	18
“ 2	J. M.	....	50 seconds	....	....	Neg.
“ 2	J. W.	....	1 minute	....	....	Neg.
“ 3	W. P.	....	20 seconds	....	....	Neg.

On the basis of blood inoculations, Marchiafava and Bignami[18] estimated the incubation period to be from eleven to eighteen days.

Mannaberg[4] describes an observation made by Sorel in which eighteen men developed malaria in from seven to nine days after their first exposure to natural infection. It seems that they were exposed to very heavy infection, which would furnish an explanation for the fact that the incubation period was somewhat shorter than that observed by others. With reference to the duration of the incubation in experimentally produced malaria, Mannaberg[4] says: "Quartan fever shows, in five cases, incubation periods of from 11 to 18 days; the average, therefore, is 13.4 days. Tertian fever shows, in seven cases, incubation periods of from 6 to 21 days; the average is, therefore, 11 days. Seven cases with parasites of the second group (ameboid, with and without crescents) show fluctuations between 3 and 14 days; the average is, therefore, 6.5 days. In two cases showing crescents without (probably with small numbers of) ameboid parasites, the incubation period was 13 to 15 days, the average being, therefore, 14."

The data available leads the author to set the limits for the vast majority of all cases of natural infection at from 6 to 21 days. It is quite possible that in rare instances it may last much longer than that, and in fact persons may become infected and carry their infection for months without ever showing recognized clinical evidence. It is possible that individuals who have so much resistance as to make this possible may finally eliminate the infection without ever having shown any clinical signs. It would even be possible for such an infection to exist and yet no parasites be found upon blood examination, because of the small number present at the time of examination. This view is especially supported by the observation that in localities where malaria is very prevalent blood examinations frequently prove considerable numbers of persons to have parasites in their blood who are not sick at the time and who have not had any evidence of malaria, so far as they know. Many of these carriers of light infection finally lose their infection without ever having clinical evidence of its presence and without undergoing any treatment whatever.

Usually there are no recognized symptoms during the incubation period. It does happen, however, that the patient may have one paroxysm of chills and fever, and sometimes two, before any malaria parasites are found in the peripheral blood. Frequently the first paroxysm is considerably milder than those following it. Although it is not possible to make a certain diagnosis of malaria until malaria parasites are demonstrated, there is no doubt that the one or two paroxysms which sometimes occur before parasites are demontsrated are a part of the disease and can therefore hardly be included in the incubation period. In those cases' which do not develop clinical symptoms early, or at all, there are of course no recognized symptoms of the incubation period. There is no doubt that the infection has a definite systemic effect. It may, however, be so slight that it is not recognized by the individual, nor could it be recognized in many instances by a most careful medical examination.

Mode of Onset and Symptoms during Progress of Disease.—The great variation in the symptoms of malaria can best be appreciated if we look upon it as an infection by parasites and not as a disease. It is simply a case of the presence of parasites in the blood and especially in certain organs and tissues of the body. The reproduction of these parasites is controlled to a large extent by the resistance of the individual. The resistance may, in some instances, be sufficient to destroy all the parasites and to prevent the production of sufficient numbers to give rise to any clinical symptoms. On the other hand, the resistance may be very poor, so that the parasites are able to reproduce at a rapid rate. A certain amount of restraint, however, is probably always present. Some infected individuals never develop clinical symptoms, as has already been stated. Whenever attacks develop, however, the onset is usually rather sudden. The patient may experience a certain amount of malaise, headache, etc., for an hour or two before the onset of the chill.

The chill is the most frequent symptom of the onset of an attack of malaria, although it is sometimes absent. It is less likely to occur in young children than in older persons. The chills of malaria almost always occur during the day, but the first one may sometimes occur at night. Such a night attack generally comes before 8 or 9 P.M. and after 4 A.M. The first chill is usually lighter than those which occur later, but sometimes it is quite severe. The duration of the chill is also extremely variable but usually lasts from a few minutes to half an hour or sometimes a little longer.

Severe headache and general aching, especially in the back and limbs, set in during the chill if they are not already present. These symptoms increase with the fever until the maximum temperature is reached. When the fever "sweats off," as it generally does, the aching usually goes with it.

Nausea and vomiting are common symptoms of the onset of a malarial paroxysm and often continue during the height of the fever.

Convulsions not infrequently occur at the onset and during a malarial paroxysm in children, especially when it is accompanied by very high fever.

The temperature begins to rise at the time the chill sets in, or sometimes from a few minutes to an hour earlier. During the chill the rectal temperature usually shows an elevation of two or three degrees. The temperature reaches its maximum within an hour or two after the onset of the chill and lasts from an hour or two to several hours in different individuals. Malaria is a disease characterized by high temperature, although in many instances it does not rise very high. Temperatures of 104° and 105° F. (40° and 40.6° C.) are the common maximum in ordinary intermittent malaria. Temperatures of 106° or 107° F. (41.1° or 41.7° C.) have been observed, although, of course, they last for only a short period of time. The fever usually lasts from two or three to six, eight or ten hours and then begins to subside rapidly with the onset of the sweating stage.

A decline in the elevation of temperature marks the beginning of the sweating stage. The patient becomes quiet and usually goes to sleep. Profuse perspiration usually lasts for an hour or more, and finally the temperature reaches approximately normal. The patient soon feels fairly well except that he is somewhat weakened and "used up" from the paroxysm. In most cases the patient continues to feel better until the onset of another paroxysm.

In simple tertian malaria the paroxysm characterized by chill and high fever lasts for from one to several hours. The symptoms rapidly subside, usually giving way to profuse perspiration. It seldom occurs that the temperature does not return to the normal before or during the night following the attack. The patient feels fairly well, except for the weakness and depression due to the paroxysm, until about forty-eight hours after the onset of the first paroxysm. Another attack of chills and fever occurs, usually beginning at almost exactly the same time of day and running about the same course, except that in persons whose resistance is not strong there is a tendency for the paroxysms to be more severe. In persons who are controlling the infection, or eliminating it, the onset of the paroxysms tends to occur later each time. On the other hand, in those who are not putting up a good fight, the tendency is for each subsequent paroxysm to set in earlier than the preceding one. In simple tertian malaria where only one crop of parasites is present, giving rise to tertian chills and fever, these attacks occur with great regularity every other day indefinitely, if not influenced by treatment, by the resistance of the patient or by some other factor. In the instance of two crops of malaria parasites segmenting on alternate days, chills and fever occur every day instead of every other day. The tendency is, however, for the paroxysm produced by each crop to occur at the same time of day as that produced by the other.

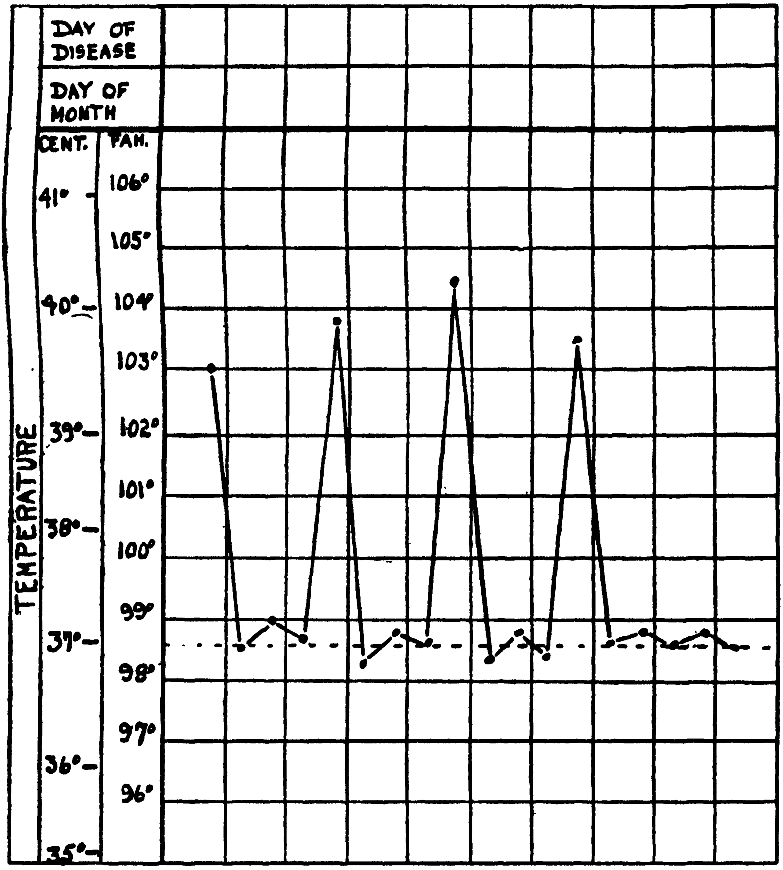


FIG. 9.—TEMPERATURE CHART OF SINGLE TERTIAN INFECTION.

In quartan malaria the onset is almost exactly like that of tertian but usually less severe. The paroxysms, both chills and fever, are also generally less severe. The duration of a paroxysm is about the same as in tertian. If only one crop of parasites is present, the paroxysm recurs at seventy-two hour periods and not at forty-eight hour periods as in tertian. It sometimes happens that there are two crops of parasites, one segmenting on one day and one on the next and none on the next, giving rise, of course, to paroxysms on those days. Sometimes, also, there may be a crop of parasites segmenting on each day, giving rise to a daily paroxysm. This occurs at the same time each day, or at least tends to do so.

The mode of onset of estivo-autumnal fever is frequently very similar to that of tertian or quartan, and there may be some prodromal symptoms; but usually the rather sudden development of a chill followed by fever is the first thing noticed. Accompanying the chills and fever are also the characteristic headache and aching in the back and limbs. Estivo-autumnal infection may give rise to intermittent chills and fever whenever the parasites segment chiefly by crops, as they generally do, or it may give rise to continued fever after the first chill occurs. In some instances we have regular every-other-day chills and fever or tertian malaria. More frequently there are two crops of parasites segmenting on alternate days, giving rise to chills and fever every day. There is a tendency for the fever to last longer following the chill; also there

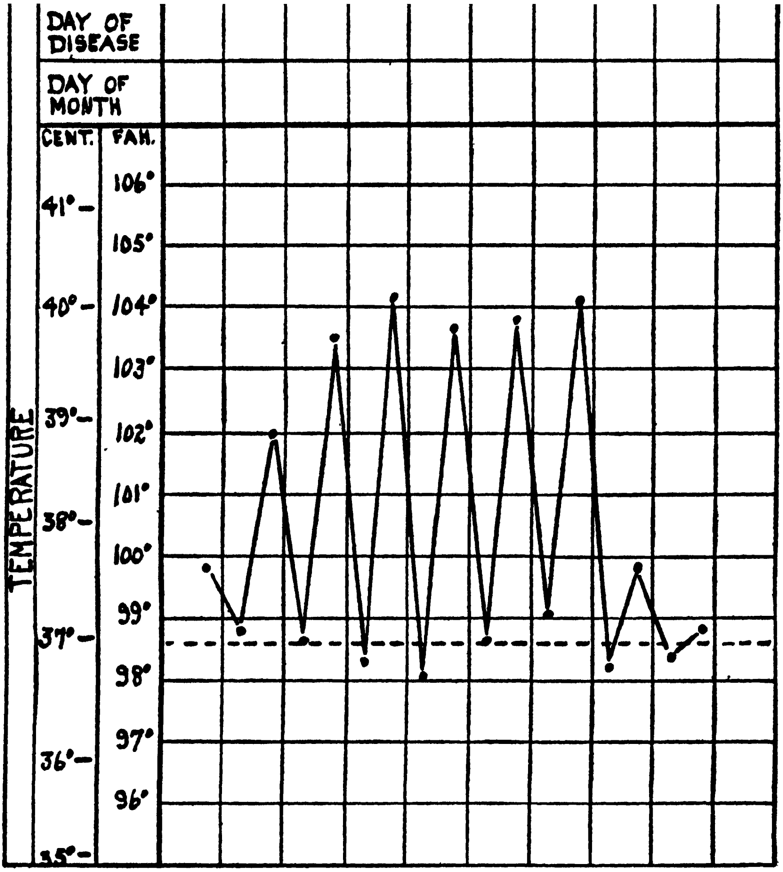


FIG. 10.—TEMPERATURE CHART OF DOUBLE TERTIAN INFECTION.

is less tendency for every paroxysm to be ushered in by chills. In the case of two crops of parasites, it frequently happens that there is more or less continuous segmentation, giving rise to continued fever, the temperature remitting, but not reaching the normal during the twenty-four hours. Usually no chills occur after the first one or two in such cases. There is no remarkable difference between the chills and fever of tertian, quartan and estivo-autumnal malaria. The noteworthy difference in the three forms is that tertian and quartan are almost always intermittent, whereas estivo-autumnal may be intermittent but is frequently remittent.

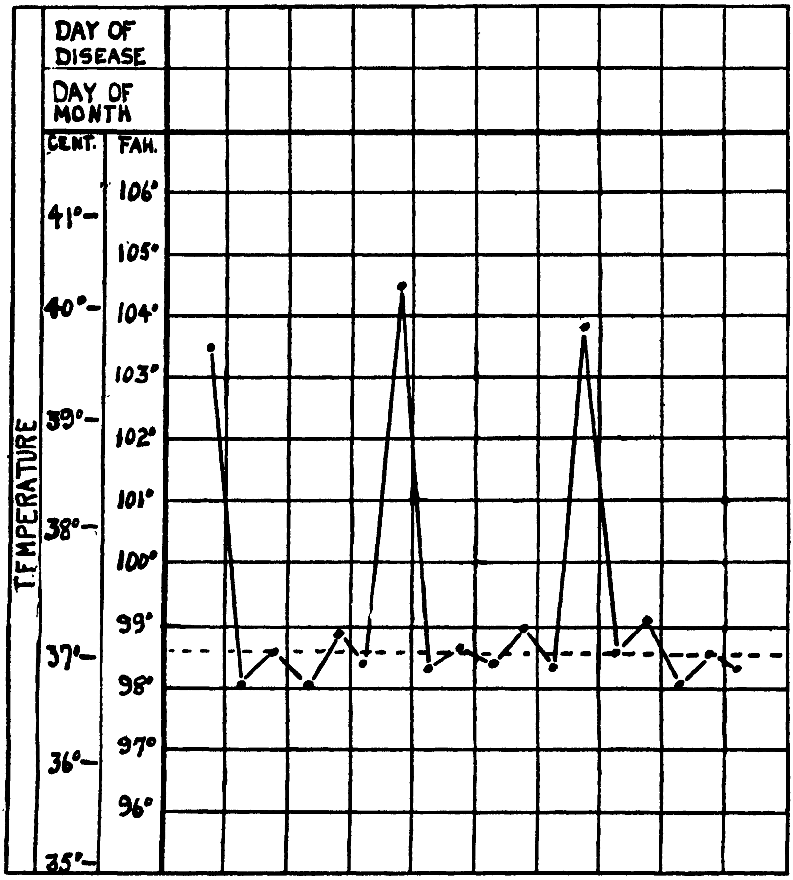


FIG. 11.—TEMPERATURE CHART OF SINGLE QUARTAN INFECTION.

In those clinical types in which the symptoms are very severe, malaria is frequently spoken of as pernicious. Nearly all cases of pernicious malaria are produced by the estivo-autumnal parasite, although occasionally the tertian or quartan parasite may produce pernicious symptoms or actually death. The so-called quotidian estivo-autumnal parasite is usually the one responsible in pernicious malaria. Sometimes the chill is especially severe and prolonged. It may or may not be accompanied by very high fever, severe gastro-intestinal symptoms or convulsions. In the event of death or threatened death due to such a case of pernicious malaria, the chill would be called a "congestive chill." The blood in such cases shows larger numbers of parasites than are usually present in the more benign clinical types. Usually the greater number of the parasites offers sufficient explanation for the greater severity.

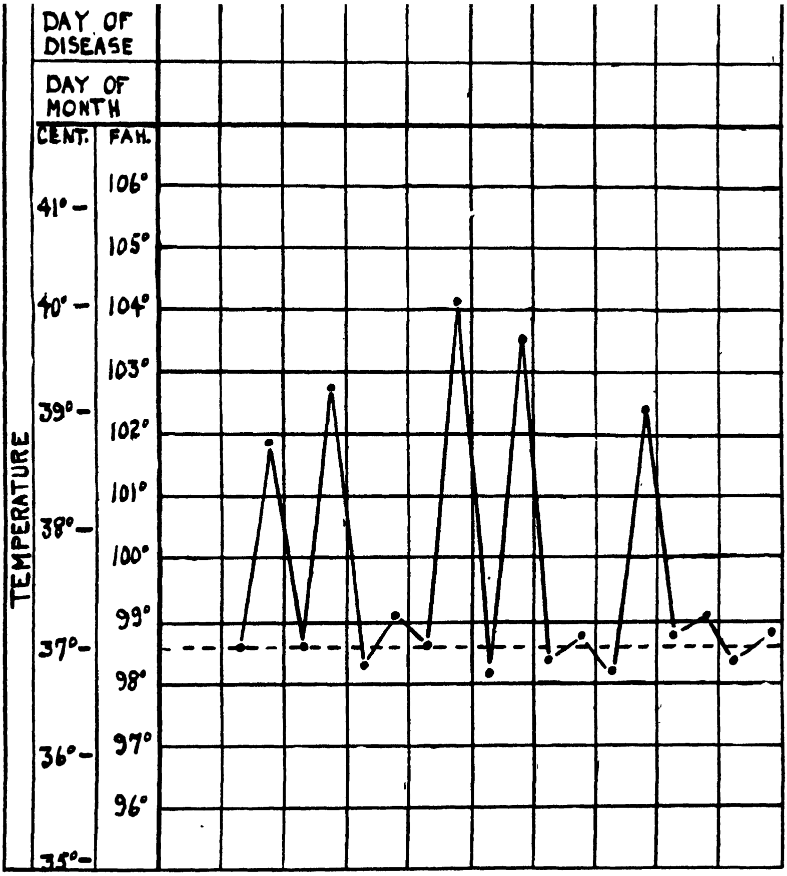


Fig. 12.—Temperature Chart of Double Quartan Infection.

Sometimes, for reasons not at present well understood, "hematuria" or, more correctly speaking, hemoglobinuria, develops. Just what occurs to produce this condition is not known. In hemoglobinuria, usually following a chill, the urine is noticed to be of a deep claret or almost coffee-black color. Great depression is usually present. Within from twenty-four to forty-eight hours jaundice begins to appear and, except in the mildest cases, develops rapidly, until the skin and sclera are a pronounced saffron yellow. In favorable cases, the hemoglobin in the *urine may clear up almost as rapidly as it set in.* In less favorable cases it may continue to increase, especially following the next chill. The chills of hemoglobinuria do not occur with the same regularity as they do in other forms of malaria. However, there is a marked tendency to periodicity, and in many instances they do occur almost as regularly as they do in ordinary malaria, chills and fever.

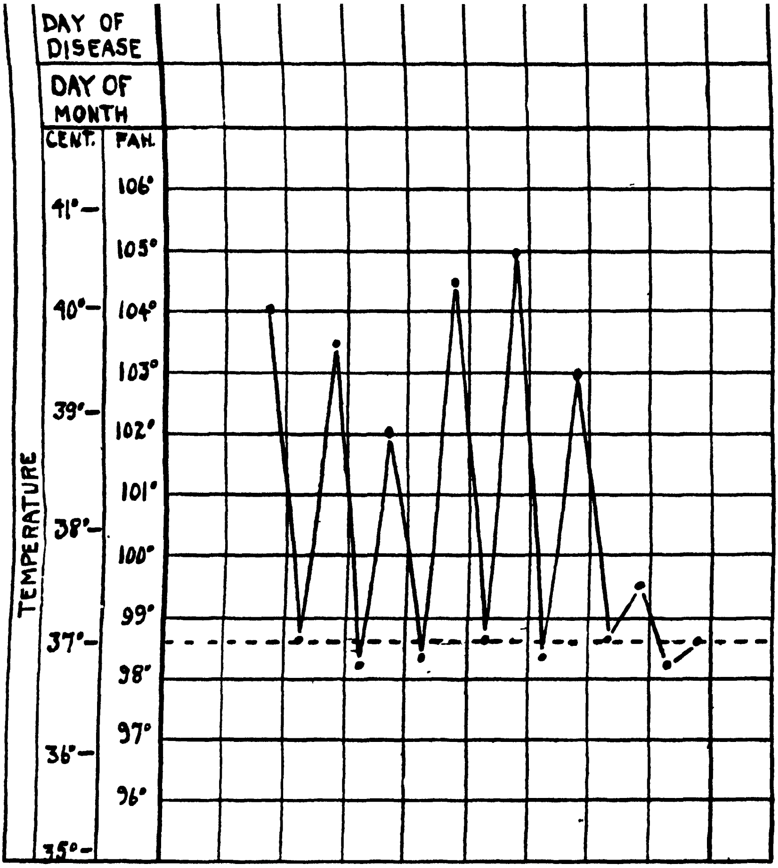


Fig. 13.—Temperature Chart of Triple Quartan Infection.

There is no uniformity in the elevation of temperature occurring in hemoglobinuria but, generally speaking, the fever is not high, ranging from 101° to 105° F. (38.3° to 40.6° C.). When the disease is progressing, it is usually remittent in type, but occasionally intermittent.

The quantity of urine decreases, accompanied by the production of casts. In cases that progress to a fatal termination, anuria almost always occurs, often several hours and sometimes several days before death. The anuria is said to be due to the plugging of the renal tubules and to diminution of blood-pressure. It occasionally happens that urinary secretion is reëstablished after more or less complete suppression for several days; in such cases recovery takes place. The depression and low blood-pressure are striking features of the disease. The blood-pressure is frequently approximately 70 or 80 mm. of mercury.

Another important form of pernicious malaria is the cerebral or comatose type. The onset is sudden, but usually it occurs in persons who have had several previous paroxysms or who have had active clinical symptoms of malaria for at least several days. It is practically always caused by estivo-autumnal parasites and varies very greatly, depending upon the number of parasites obstructing the capillaries of the brain, and upon the extent and location of the obstruction. No doubt some parasites lodge in the brain in all cases of malaria, but whenever they are sufficiently numerous, sufficient anemia of the brain is produced to cause coma. The profoundness of the coma varies very greatly, of course, as does also its duration. Sometimes it lasts only a few hours and passes away with the subsidence of the high fever. In other instances it continues and increases until the death of the patient, in spite

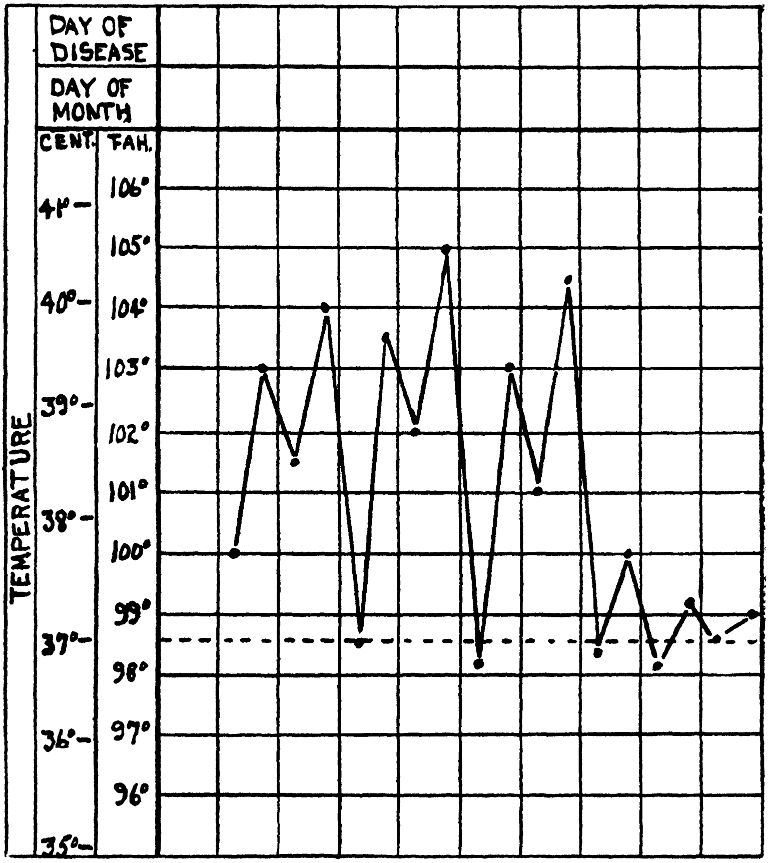


Fig. 14.—Temperature Chart of Tertian Estivo-autumnal Malaria.

of any treatment given. Usually there are very large numbers of parasites present in the blood in these cases. In such instances delirium and unconsciousness are present, especially during the high fever period. They generally subside with the fever.

Physical Findings.—It must be understood that malaria consists of an infection with one or more of three different species of malaria parasites, each of which produces somewhat different symptoms and may have a somewhat different effect, recognizable on physical examination. It must also be understood that the number of these parasites in different individuals may vary very greatly, from a number entirely too small to produce any recognized effect up to one sufficient to produce death. Between these two extremes there will be wide variations in the symptoms and findings upon examination. For instance, in the case of individuals who have been infected with malaria parasites but have sufficient resistance to prevent their multiplying to any considerable extent, it may be that nothing abnormal can be recognized by a physical

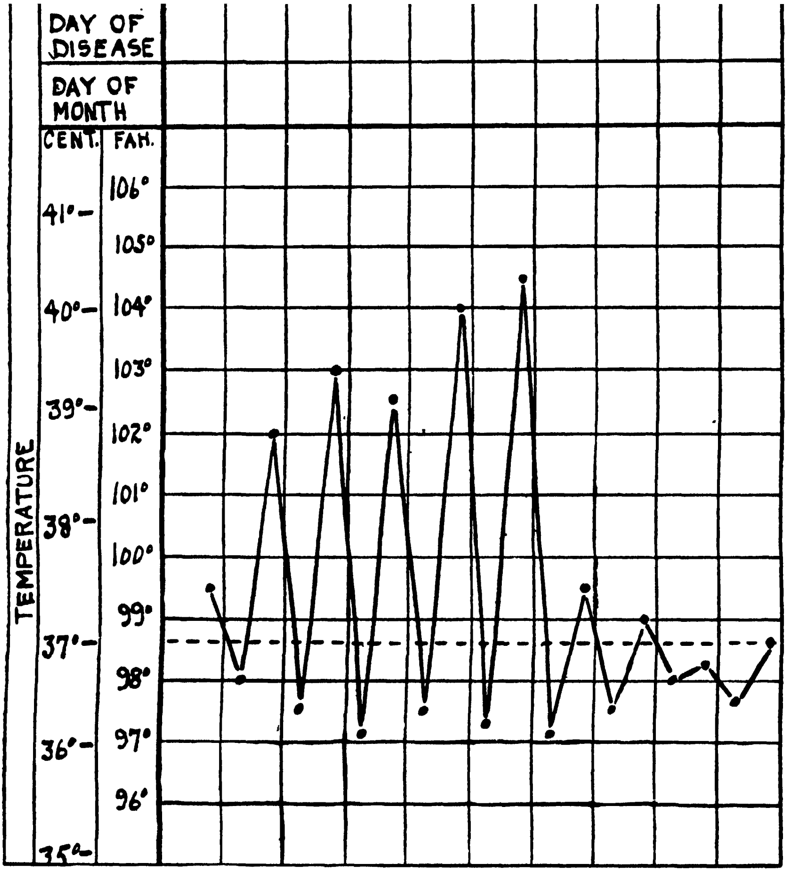


Fig. 15.—Temperature Chart of Quotidian Estivo-autumnal Malaria.

examination. There are, however, changes demonstrable by physical examination in practically all infected persons who have clinical symptoms due to malaria.

Observation.—During the first few days of a first attack of active malaria nothing abnormal may be recognized by observation. After a few paroxysms have occurred, however, there has usually been sufficient destruction of blood-cells so that a certain amount of anemia is present. As the disease continues, the anemia increases more or less, and sooner or later it will be noticed from the general appearance of the individual, as well as upon examination of the mucous membranes. Repeated paroxysms, or chronic malaria, result in a sufficient collection of the malaria pigment in the capillaries of the skin to give rise to a more or less muddy, cachectic appearance. This cachexia may be very marked in those who have had repeated attacks for long periods of time, especially when the attacks are due to estivo-autumnal parasites. The other parasites do not give rise to cachexia to anything like the same extent as the estivo-autumnal type. In fact, almost all cases of malarial cachexia are due to estivo-autumnal infection.

In the hemoglobinuric form, if it is at all severe, hematogenous and perhaps hepatogenous discoloration of the skin appears soon after the appearance of the hemoglobinuria. In severe cases this is frequently very marked and the appearance of the patient is quite similar to that of one suffering with yellow fever. In addition to this hematogenous change which is found more or less in cases of hemoglobinuria, there is sometimes sufficient hepatitis in other forms of malaria, where for some reason or other the parasites especially localize in the liver, to give rise to considerable bile-staining of tissues and to a jaundiced appearance.

In the pernicious, comatose cases the patient is observed to be in a more or less profound state of coma. Usually the pupils are dilated.

Palpation.—One of the positive changes revealed by palpation in malaria is the enlargement of the liver which occurs in a large proportion of all cases that have continued for any considerable length of time. In chronic, cachectic cases, especially in those of long standing, the border of the liver is usually readily palpated well below the costal border. It is firm and hard but not so strikingly so as the accompanying enlarged spleen.

The other change to be recognized by palpation is in the spleen which is enlarged and hard in most cases of malaria where clinical symptoms have continued for more than a few days. The spleen is enlarged in all cases of clinical malaria and in all forms of the disease, but the enlargement is greater in the tertian and estivo-autumnal form than in the quartan. During the first few days of a first attack of malaria it may be impossible to palpate the spleen, but after that the border can usually be felt extending more or less below the costal border, depending upon the duration and severity of the attack and perhaps also upon the individual case and the type of infection. In chronic cases of long standing it is not uncommon for it to extend below and to the right of the umbilicus. These very large spleens are usually extremely hard. In most instances they can be felt without difficulty, and if the abdomen is at all relaxed one can usually grasp the organ in the hand and palpate it with great ease. In such cases, the patient himself frequently feels and recognizes the enlarged spleen.

The spleen can be palpated best with the patient in the recumbent position and with the knees drawn up to relax the abdomen. The *technic* is as follows: Stand on the right side of the patient and place the left hand over and beyond the region of the spleen so as to be able to lift it forward against the costal border and abdominal wall. Now with the right hand placed flat upon the abdominal wall, do the palpating with the tips of the fingers. Instruct the patient meanwhile to take a full inspiration and then to exhale. Repeat this two or three times in order to accustom the abdominal muscles to the hand on the abdomen and to obtain thorough relaxation. As the patient takes a full breath after having exhaled, lift the spleen forward with the left hand and gently press the tips of the fingers of the right hand against it. About the middle of the inspiration and after the spleen has been forced against the finger tips, which are pushed forward to meet it, raise the fingers somewhat and allow the spleen to slip beneath the finger tips. The sensation produced is striking and enables one to recognize the spleen without difficulty.

The frequency of enlargement of the spleen is so great in some countries that it is calculated as a means of determining the prevalence of malaria in the region. The author's observation has been that the spleen rate would be of little value in determining the endemic index in this country. It must be granted that it may be useful in other countries where malaria is much more prevalent than it is here, but it does not seem advisable to substitute it for the more dependable blood examination for this purpose.

Percussion.—Percussion does not reveal anything in malaria, but it may be an aid in outlining the size and location of the liver and spleen. Usually palpation is much more dependable, particularly for the purpose of recognizing enlargement of the spleen. Percussion is especially useful in determining the border-line of liver dullness.

Auscultation.—There is nothing abnormal to be found by auscultation in malaria except perhaps in the extremely rare, so-called pneumonic form, in which there are large numbers of parasites lodged in the capillaries of the lungs. Râles and other evidences of hyperemia may be found, but it is always doubtful whether they are due entirely to the malaria or to secondary or accompanying conditions. There is no reason why there should not be cases of malaria and pneumonia occurring simultaneously in the same individual. In fact, such is the case, and the author doubts whether there is such a form of malaria as the pneumonic form, due to malaria only.

Special Tests—Reflexes, etc.—In comatose and other pernicious forms of malaria the reflexes may be diminished and there may be paresthesia. These are to be found especially in extreme cases. If we understand that a large proportion of such cases, if not all of them, are caused by the collection of large numbers of parasites in the capillaries of the brain and perhaps of the cord, and by the localization of the parasites in different parts of these particular organs, we will be prepared to expect various nerve phenomena in different cases. Delirium, tetany, tetanic or convulsive paroxysms upon irritation may occur in rare instances.

LABORATORY FINDINGS.—1. *Blood.*—Laboratory examinations of blood in malaria show many changes, varying with the intensity and duration of the infection. In many instances the resisting influences of the body are strong enough to prevent sufficient reproduction of malaria parasites to give rise to demonstrable effects upon the blood. On the other hand, in cases where there is very active multiplication of the parasites and consequent destruction of the red blood-cells, more or less anemia is produced. In the severer cases anemia is present to a very large degree. It is not uncommon to find hemoglobin readings as low as 50 or 60 per cent., and in some instances even as low as 40 per cent. This low reading is sometimes reached in a comparatively short time in the worst cases. Not only is there reduction in the hemoglobin reading, but there is also more or less reduction in the total count. Usually the count does not decrease as rapidly as the hemoglobin percentage does, and therefore we always have a color index below normal in uncomplicated malaria. In the severer cases, polychromatophilia, stippled and occasionally nucleated cells are found. Bad chronic malaria cases show almost as much granular degeneration of the red cells as any other condition except lead-poisoning, pernicious anemia and some of the leukemias.

The only change in the leukocyte count is an increase in the percentage of the large mononuclear cells. In most cases of malaria in which there are active clinical symptoms the count runs from about 6 per cent. to 15 per cent. or 18 per cent., sometimes even higher. It is not uncommon to find malaria pigment in the large mononuclear or endothelial leukocytes. Whenever the pigment is found, it is quite characteristic and diagnostic.

Malaria parasites are found in the blood in practically all clinical cases of malaria which have not been recently treated by quinin. Quinin causes the rapid disappearance of parasites, especially of the schizonts, and therefore in interpreting the presence or absence of parasites in a given case, one should always take into consideration information as to whether or not quinin has recently been taken. Even five or ten grains of quinin are frequently sufficient to cause the disappearance of parasites. The latter sometimes disappear as a result of quinin a short time before the disappearance of the clinical symptoms. In malaria patients who take sufficient quinin to cause the parasites to disappear from the peripheral circulation, the fever, or chills and fever, do not continue for any length of time after the ingestion of the drug.

(*a*) *Technic of Blood Examination for Malaria Plasmodia.*—There are three methods of examining the blood for malaria plasmodia, each one of which has its advantages and application: (1) the ordinary "thin film method"; (2) the "thick film method," and (3) the "centrifuge method." The thin film method may be learned quickly and is by far the most practical for all ordinary purposes. The thick film method requires much more experience on the part of the operator, and in the hands of those with little experience, it is less reliable. In the hands of experienced workers, however, it results in great saving of time. From about three to ten times as much blood can be examined in a given length of time by this method as by the thin film method. Only those with special facilities and training are able to use the centrifuge method with success. When properly carried out it frequently results in the finding of parasites in blood when they could not be found by any other method. However, it is not to be recommended for general use.

Thin Film Method.—Prick the finger or ear lobe (a straight, Hagedorn needle makes a good blood sticker) and squeeze out approximately ¼ drop of blood. Touch this with the surface of a clean microscope slide at about the junction of the middle and outer third of the slide. Place the end of another slide in the drop and spread it out thinly. Most of the spread should be on the middle third of the slide. It should vary in thickness from too thick to see through on one end to as thin as possible on the other end of the spread. The blood spread dries quickly and should then be labeled by writing the name or initials of the patient across the face of it either with an ordinary lead pencil or, preferably, with a metal point (such as the blunt end of a needle). Such preparations may be kept for hours, days or weeks before they are stained and examined. However, better results are obtained if they are stained within from twelve to twenty-four hours after the time they are made.

There are many different stains that are quite satisfactory, various modifications of the Romanowsky stain being the best. Wright's stain is almost perfect for this purpose. The technic of staining is as follows:

(1) Cover the preparation with the stain for one minute.

(2) Dilute the stain on the slide with from one to four or five times as much water, preferably distilled, and allow to remain from three to five minutes.

(3) Wash off, dry and examine with the oil immersion lens.

Thick Film Method.—For the thick film method blood is obtained in the same way, but a somewhat larger quantity is drawn. From one-half to one drop is preferred. Instead of being spread out thinly on the slide, the blood is made into a thick film by spreading it out somewhat with the corner of another slide. Usually half a drop of blood will make a spread of proper thickness, about half an inch in diameter. It should be as thick as can be decolorized and stained properly and examined satisfactorily. Experience will be the best guide as to the proper thickness.

Several different methods of decolorizing and staining these thick film preparations have been recommended. A perfectly satisfactory one is as follows:

(1) Decolorize and fix the preparation in methyl alcohol (Merck's highest purity), containing 2 per cent. glacial acetic acid and 2 per cent. hydrochloric acid. It takes from one to three minutes to decolorize recently made preparations. Very old preparations are much more difficult to decolorize.

(2) Wash, preferably in running water, to entirely remove the acid. This requires only a minute or two.

(3) Stain in the polychrome methylene blue solution described below, for two or three minutes.

(4) Transfer without washing and stain in 1 to 1000 solution of eosin in water, for one-half minute.

(5) Transfer without washing and stain again in the polychrome methylene blue solution for one-half minute.

(6) Transfer without washing and dip once only into the eosin solution, after which wash immediately in running water. Allow the preparation to dry and examine with the oil immersion lens. Malaria parasites stain well, but have not exactly the same appearance as they have in the thin film because of the fact that they are not spread out, or rather that the red blood-cells containing them are not spread out flat on the slide. The platelets are stained more or less and there is also considerable foreign material and débris which may mislead one not familiar with malaria parasites in such a preparation.

Stock polychrome methylene blue solution is made by heating a 1 per cent. solution of methylene blue in water containing ½ per cent. of sodium bicarbonate, in a steam sterilizer for one hour. This is filtered and is known as stock solution of polychrome methylene blue. The staining solution is made by adding 2 c.c. of this stock solution to 100 c.c. of water. The dilute solution may be used for several days before making up a new staining solution.

The Centrifuge Method.—This method depends upon the fact that when defibrinated or citrated blood containing malaria parasites is centrifugalized under proper conditions, all the large parasites rise to the surface of the cell-column in the bottom of the tube.

Blood is drawn from the vein by means of a clean, dry syringe (or of a hollow needle only) and defibrinated by stirring it with a suitable glass rod or other instrument. Another equally satisfactory method of preventing coagulation is the addition of 2 c.c. of a 50 per cent. solution of sodium citrate to 10 c.c. of blood immediately after it is drawn.

Place the defibrinated or citrated blood in large centrifuge tubes so that the depth of blood is from 2 to 5 cm. Centrifugalize at about twenty-five hundred revolutions per minute for from one to three minutes. Most of the large parasites come to the top of the blood-cell column and may be removed with many blood-cells by very careful "skimming" by means of a small capillary pipet fitted with a rubber nipple. Place the blood skimmed as suggested on a slide and spread either for a thick film or for a thin film, according to which is desired. Stain and examine as described above.

For a description of the parasites as found in the blood, *see* page 571. For the interpretation of laboratory findings in the diagnosis of malaria, *see* Diagnosis.

2. *Urine.*—In persons who have malaria but who are resisting the infection sufficiently to prevent clinical symptoms, no change in the urine can be recognized. This is especially true in the tertian and quartan form.

Polyuria during and just preceding the paroxysm is the rule with all mild or ordinary cases of malaria. The fever stage is accompanied and followed by highly colored urine, usually reduced in quantity. It is probable that this is the result of the fever and sweating, as it is also produced by fevers and sweats caused by other diseases. Deaderick[5] states that there is a polyuria of convalescence—"post-malarial polyuria." He says further, "The polyuria of convalescence ordinarily begins from three to six days after the attack and continues for from a few days to several weeks."

The output of urea is increased in malaria as in other fevers. There is usually an excess of iron present, especially following the paroxysm.

In mild cases of malaria, albuminuria is relatively infrequent. On the other hand, in severe cases and especially in pernicious malaria, albumin is usually present in varying quantities. Generally speaking, the more severe and more pernicious cases show the largest amount of albumin.

Casts are not often found in mild cases, but in the severer and especially in the pernicious cases both hyaline and granular casts are often present. As would be expected, the more albumin the more casts, in most instances.

It is true that casts and albumin are present to some extent in almost every case of comatose malaria, but this does not indicate that the coma is due to uremia. It is produced in an entirely different manner.

In hemoglobinuric fever most important and significant changes are found in the urine. The individual whose urine, only a few hours previously, was clear, with little or no albumin and casts, will have a chill. The first urine voided afterward will vary in color from light claret to coffee black. When examined in a thin layer by transmitted light it appears of a lighter red color. When examined in a thick layer it may be as dark as black coffee. The hemoglobin is in the form of methemoglobin, though oxyhemoglobin is later formed. Chemical examination shows the presence of hemoglobin.

Albumin is present in varying but usually in very large quantities. The albumin content is not due entirely to the presence of blood, but there is acute nephritis, which increases the quantity of albumin over what would otherwise be present.

Microscopic examination reveals a great deal of sediment and débris resulting from the inflammatory process in the kidney. Some blood-cells are usually found, but they are not present in sufficient numbers to explain the color nor to justify the diagnosis of the condition as hematuria. It is not a true hematuria but a hemoglobinuria. Casts are present, usually in large numbers, and there are many granular and epithelial casts, indicating the most destructive form of nephritis. There is nothing that impresses one with the true nature of the condition and with its gravity more than does an examination of the urine sediment, especially in those cases in which no great amount of urine is eliminated. One realizes that the tubules of the kidneys are simply plugged or stopped up and that there is great danger of suppression, which occurs in most of the fatal cases of hemoglobinuria. Sometimes the anuria lasts for several days before death. In rare cases, after a few days of anuria, the elimination starts up again, but patients seldom recover if the anuria lasts more than twelve or twenty-four hours.

In cases of hemoglobinuria which end in recovery, and also in pernicious cases in which there are albumin and casts, these continue to be present for several days or weeks, gradually decreasing until they finally disappear entirely, except in a few instances in which the nephritis continues. This probably occurs only in those individuals who for some reason or other are especially prone to the development of nephritis. Some of them would sooner or later have developed it without the influence of the malaria attack.

3. *Stomach Contents.*—The stomach contents are not affected in ordinary cases of mild malaria. On the other hand, in severe attacks, especially of pernicious malaria, the functioning capacity of the stomach may be greatly reduced or almost absent. Stomach tests are not made under these circumstances, but if they were, the total acidity and free hydrochloric acid would be found to be greatly reduced. Slow or imperfect gastric digestion would also be in evidence.

In pernicious malaria, especially in the gastric form, vomiting is a frequent symptom and the vomited material lacks its normal acidity.

In hemoglobinuria, the gastric contents almost always give a reaction for occult blood, and upon microscopic examination are found to contain blood-cells. In many pernicious gastric cases there is sufficient hemorrhage into the stomach, as a part of the general process, to give rise, in case of vomiting, to the so-called black vomit, resembling that of yellow fever.

4. *Feces.*—There is no change in the feces of persons who are infected with malaria but who have no clinical symptoms, nor is there any demonstrable change in ordinary, mild cases of malaria. In pernicious cases, especially in the intestinal form in which the normal function is very largely hindered, the feces are liquid as a symptom of the diarrhea.

In hemoglobinuric fever the feces almost always give a reaction for occult blood, and in the severer cases there is frequently a great deal of blood or hemoglobin present.

5. *Transudates and Exudates.*—In long standing, chronic cases of malaria in which there is great enlargement of the liver and spleen, there is frequently more or less ascites. The fluid is of a dark yel-

lowish color considerably darker than the fluids seen in ascites from other conditions.

6. *Milk.*—Malaria has no effect upon the milk except that in the most severe forms the flow is greatly reduced or entirely stopped. No examination is made of milk in connection with malaria.

7. *Tissue.*—No tissue examination is made for a diagnosis of malaria except that of material obtained by spleen puncture, which will be discussed under Special Examinations, Spleen Puncture. Sections of tissue from any part of the body would show malaria pigment in the endothelial cells lining the capillaries, but this is not made use of in diagnosis because of the convenience of the very much more practical blood examination. Sections of skin in all chronic cases of malaria, especially if cachexia is present, show malaria pigment. This is what gives to the skin its characteristic appearance in malaria.

SPECIAL EXAMINATIONS.—1. *Functional Tests.*—In ordinary cases of malaria the renal functional tests would show nothing. In fact, they are not resorted to in diagnosis in connection with malaria. However, in all cases of malaria, especially those in which there is renal involvement, there is great reduction in the elimination by the kidneys.

2. *X-ray Examinations.*—*X*-ray examinations are not indicated nor practiced in malaria. It would be possible to demonstrate the enlargement of the spleen and liver by this means, but it is much easier to do so by the usual methods of physical examination, especially palpation and percussion.

3. *Spleen Puncture.*—Puncture of the spleen and microscopic examination of the material obtained has sometimes been resorted to in examining for malaria. There is considerable difference of opinion as to whether or not this method is justified. The author agrees with the advice of Craig[19] that this procedure should not be resorted to for the purpose of diagnosing malaria. It is a dangerous and unnecessary procedure. There is always the possibility of tearing the capsule by a sudden movement while the needle is in the spleen and in such event a dangerous hemorrhage may occur.

Diagnosis.—CLINICAL HISTORY.—There is perhaps no disease in which the clinical history is of more value in indicating the diagnosis than it is in malaria. It is not possible to make an infallible diagnosis without the confirmation of all other evidence by the demonstration of malaria parasites. It is, however, possible, in many instances, to make about as certain a diagnosis on the basis of the clinical history as in any other disease. This applies, however, only to the simple, ordinary cases of malaria, especially in the intermittent form. The clinical history does not help much in the diagnosis of malaria infection in individuals whose illness does not assume the usual clinical forms, especially in those who are malaria carriers but have no clinical symptoms whatever. The following are some of the more important points in the clinical history that may indicate malaria:

(*a*) *Residence.*—The individual who lives in a region or locality well known to be malarious or one who has lived in such a region during several years preceding the attack is likely to have malaria, but if he has lived entirely away from a malarious region for more than one or two years without having had attacks during the time, this is strong indication that the disease present at the time is not malaria. Those who live in the country in malarious regions are much more likely to have malaria than those who have lived in cities and large towns, because there is not much transmission of malaria except in the rural districts.

(*b*) *Family History.*—It may seem strange that family history should play any part in the diagnosis of malaria, but it is of some value. Of course it is of minor importance compared with the laboratory findings. When the patient is living with his family, members of which have recently had attacks of malaria, he is especially likely to have it himself.

(*c*) *Occupation.*—A history of an occupation which would lead to special exposure to malaria infection would tend to support a diagnosis of malaria in the presence of other evidence. For instance, persons engaged in logging at a camp or mill where malaria is known to be prevalent, or engaged in work on streams and in swamps where the conditions for the transmission of malaria are most favorable would be much more likely to contract the disease than those whose occupation did not expose them to the same extent. Therefore, the history of such an occupation would tend to support or indicate the diagnosis of malaria.

(*d*) *History of Previous Illness.*—The history of previous attacks of malaria or attacks of diseases in which the diagnosis was not made but which were probably malaria tend to indicate the presence of this disease at the time of examination. Malaria relapses are so frequent as to make a positive history of previous attacks especially indicative.

(*e*) *Present Illness.*—Those who have acute or active clinical malaria give about the most clear-cut history of any disease that we know. Chills and fever, intermittent and periodical, occur in more than 50 per cent. of all cases of clinical malaria. Practically all cases of the tertian type who are really sick have chills followed by more or less fever for a few hours, and later by a period of normal temperature. There is no other disease in which the characteristic intermittent, periodical chills and fever occur. Quotidian, tertian and quartan clinical types are all characteristic. The remittent fever produced sometimes by quartan but nearly always by estivo-autumnal infection is much more difficult to recognize by the clinical history of the illness. The attack may begin with a chill, but continue with intermissions for days without another chill occurring. Malaria should always be suspected in such cases unless there is some other very clear explanation of the condition.

One striking thing about the history of attacks in malaria is the fact that almost all malarial chills occur during the day. It is extremely rare for a malarial chill to occur at night. A chill occurring during the night, therefore, is almost certain to be due to some disease other than malaria. A few years ago, during an epidemic of yellow fever in a town (Tallulah, Louisiana) in which malaria was also quite prevalent, the author was impressed with the importance in diagnosis of the history of the time of day at which the first chill occurred. Of course the physicians did not depend upon the clinical history alone in making the diagnosis, nor as a means of eliminating malaria in suspected yellow fever cases. Yet it was striking how frequently this data enabled them to differentiate between the two diseases, after the appearance of the first chill, before making the microscopic diagnosis. The first and only chill in yellow fever occurs at night in a large proportion of the cases, and the first and all other malarial chills nearly always occur during the day.

Although there are many other diseases in which one or more chills may occur, followed by elevation of temperature, it should be a rule with all physicians that a chill and fever, the cause of which is not apparent, call for a blood examination for malaria as well as for other examinations.

Physical Findings.—During the first few days of a malarial attack a physical examination may fail to reveal anything that is diagnostic or strongly indicative of malaria. After the disease has lasted for more than a few days, more or less pigmentation or muddy discoloration of the skin and tissues takes place. This is due to the phagocytosis of malaria pigment by the endothelial cells of the capillaries. It is only in the cases in which there are a great many parasites present that this is at all noticeable.

In the hemorrhagic form of malaria one frequently recognizes the lemon yellow tint of the skin and mucous membranes. It is usually very striking in the severer cases.

The tongue is broad and furred in most cases of acute malaria. There are so many other diseases in which the tongue has the same appearance that this condition can be of little diagnostic value.

In chronic cases of malaria the liver is usually somewhat enlarged, but this is not of much diagnostic importance because of the fact that the same thing occurs in a great many other diseases and conditions.

Enlargement of the spleen occurs in a large majority of all chronic cases of malaria where clinical symptoms are produced. However, many people are infected with malaria for months or years without having any demonstrable enlargement of the spleen. Those who suffer from frequent clinical attacks have a spleen that is palpable below the costal border or even much further. The diagnostic importance of an enlargement of the spleen is reduced by the fact that whenever malaria has been sufficiently active to cause much enlargement, the clinical history is usually so definite and clear-cut that the diagnosis is strongly indicated. Malaria should always be suspected and looked for, however, in the presence of an enlarged spleen.

Laboratory Findings.—The only way in which an exact and absolute diagnosis of malaria can be made is by a microscopic examination and the demonstration of malaria parasites in the blood. The clinical history may indicate malaria, physical findings may also indicate it, but no absolute diagnosis can be made until parasites have been demonstrated in the blood. Barring extremely few rare exceptions, whenever the patient has sufficient malaria parasites to give rise to clinical symptoms, the parasites can be demonstrated in the blood by competent examination. These rare exceptions are usually cases in which only one chill has occurred, the parasites not always being demonstrable until after the second and sometimes even the third chill.

Malaria parasites can be diagnosed with absolute certainty by one who is familiar with them, and whenever they are found it always means that the patient has malaria. It does not, however, necessarily mean that malaria is the cause of the illness present at the time. Other diseases may be complicated with malaria or occur in individuals who have malaria infection, as well as in other persons. It may occur and does occur that malaria carriers who have few parasites and who show no clinical symptoms at all suffer from other diseases; yet blood examination may show the presence of malaria parasites. There is a tendency for the parasites to produce malaria symptoms in addition to the symptoms of whatever other disease co-exists, although up to that time the patient has shown no malarial symptoms whatever. It is quite possible for one to be misled by such a case in which the malaria parasites are quite numerous and malarial symptoms are added to the other clinical features of the case. On observing such a case for the first time, one would perhaps be likely to overlook the accompanying disease unless it happened to be one in which the symptoms were prominent and characteristic.

In interpreting a negative laboratory examination for malaria in persons who have clinical evidence of the infection, one must not overlook the misleading influence of quinin. Many patients, especially those living in malarious regions, have already taken quinin before a physician is consulted, or it may be that quinin has been prescribed by the physician before the blood examination is made. Large doses of quinin cause the disappearance of asexual parasites in from twelve to about seventy-two hours in all cases of malaria, provided the dose is large enough. This is true of all forms of malaria except, occasionally, the pernicious cases, especially those which have been comatose.

The asexual parasites may continue to appear in the blood for four or five days in rare instances after quinin has been started. The gametes in tertian and quartan malaria usually disappear rather rapidly, usually within three or four days after quinin treatment has been begun. The gametes of estivo-autumnal are more resistant to quinin, and are probably little affected by it. It usually takes from one to two weeks of treatment for all of the organisms to disappear. It is not likely that new gametes are produced after large and proper doses of quinin have been administered, but it takes from one to two weeks for the estivo-autumnal crescents to die out after the patient starts taking sufficient quinin to prevent the production of others. The fact that malaria parasites are not so likely to be found in cases of malaria in which quinin has been administered as in those in which none has been given, is no argument against the examination of the blood whenever malaria is suspected. Parasites are usually present as long as clinical symptoms continue. Given a patient with fever or chills and fever due to malaria, it is almost certain that there are parasites in his blood. Quinin causes the disappearance of clinical symptoms, usually earlier than it does the disappearance of parasites. Whenever an examination is made under these circumstances a positive examination is of just as much value as if the patient had not taken quinin, but a negative report is not of anywhere near as much negative value as it would be if quinin had not been taken.

Complications and Association with Other Diseases.—So far as the writer knows, there is not a single disease the presence of which prevents the presence also of malaria. Therefore malaria may be complicated by or associated with any other disease or condition to which man is susceptible. The diseases which are most likely to complicate or be associated with malaria would naturally be those diseases which are most prevalent in that particular region in which it occurs. Individuals who have malaria may have pneumonia, tuberculosis, typhoid fever or any other disease, but since malaria is a disease found most commonly in warm countries, it is more likely to be complicated by other diseases especially prevalent in the warm climates, such as, for instance, hookworm and other intestinal parasite diseases. Whatever diseases are associated with malaria do not occur because of the presence of malaria, but incidentally or coincidentally with it.

Other diseases do not greatly alter the course of malaria except that their symptoms may mask the symptoms of malaria to such an extent that it is overlooked. The possibility of malaria being associated with other diseases in any region where malaria prevails to any great extent is so great that, in the author's judgment, a blood examination for malaria is indicated in practically all acute sicknesses. There is no other way of definitely proving that malaria is not present. In fact, a negative blood examination only shows that there is no active malaria present at the time. Whenever malaria is associated with other diseases, the treatment, so far as malaria is concerned, is not altered in any way, except that in special instances quinin may possibly be objectionable. A case will rarely occur, however, where quinin is more harmful than malaria.

Surgical operations, injuries, childbirth, etc., are likely to cause the development of acute malaria in individuals already infected. The development of fever in such cases in regions where malaria prevails always demands a blood examination for malaria. In the event that the disease is present, the choice between quinin treatment and malaria is usually not difficult to make.

The author wishes to mention one complication, not because of its great frequency, but because it often misleads the physician as to the effect of treatment. He refers to the chills, fever, sweats and leukocytosis sometimes produced by inflammation or necrosis of tissue due to injections of quinin. The inflammation or necrosis may be due entirely to the action of the drug and not to infection. Symptoms usually begin from four to seven days after the injection and vary in severity and duration with the damage done to the tissues. Often the physician mistakes them for active symptoms of malaria and erroneously concludes that the quinin treatment has failed to relieve the active symptoms of the disease. This complication only occurs where treatment by injection of quinin is practiced and fortunately there seems now to be a tendency at least to use the method less than formerly. It is to be hoped that the reform in this direction will continue.

Sequelæ.—There are no sequelæ in ordinary cases of clinical malaria or in the case of malaria carriers who never develop clinical symptoms, provided proper treatment is carried out. Chronic malaria in which the patient has repeated attacks of considerable duration, and pernicious malaria of whatsoever type, including especially hemoglobinuria, are the forms in which there may be sequelæ.

It is stated that *myocarditis* frequently occurs as a result of attacks of pernicious malaria, and this is especially to be expected in the hemorrhagic form. The myocarditis may last for a considerable time, accompanied by the usual symptoms of lack of compensation, etc.

The *enteritis* or *dysentery,* in the pernicious cases in which there is especial collection of the parasites in the tissues of the gastro-intestinal canal, is likely to be more or less chronic, regardless of the disinfection of the individual. These symptoms remain as sequelæ for many years. Although they may not be present at all times, provocation may bring them on from time to time.

Cirrhosis of the liver as a sequela of malaria is rare in the southern states, and probably everywhere else where malaria is of the similar mild type, especially where there is sufficient intelligence to lead to considerable use of quinin. On the other hand, in the tropics, where many persons have chronic malaria and malaria cachexia for months and years, cirrhosis of the liver is said to be much more frequent. It seems reasonable that such would be the case.

There is perhaps more or less *nephritis* during the acute stage of all pernicious cases of malaria. It is much more marked in the hemoglobinuric form, in which the nephritis is frequently sufficient to cause complete suppression of urine. The tendency is toward rapid recovery, but this is perhaps less frequent in the hemoglobinuric cases. In some instances it continues in a chronic form as a sequela of the disease. Amyloid degeneration may also be a renal sequela.

Neuritis and *paraplegia* have been attributed to malaria and may possibly sometimes be produced by it. It is more likely that in most instances they are simply associated conditions. Seven years ago the author observed a case of hemiparesis which occurred coincidentally with an acute attack of estivo-autumnal malaria. The hemiparesis cleared up in four or five days after the temperature returned to normal as a result of quinin. Most of the effects upon the nervous system tend to rapidly clear up after quinin treatment is instituted, and they are not likely to remain as sequelæ.

Amaurosis and blindness sometimes occur during attacks of malaria and remain indefinitely. There is some difference of opinion as to whether these are due to the effects of malaria or to the quinin treatment for the disease. There can be no question that quinin is, in certain rare instances, quite damaging to the optic nerve, producing endovasculitis of the nerve-vessels. There may be more or less permanent thickening and atrophy of the visual path. Davis[20] says that "the original effect is upon the vasomotor centers, producing constriction of the vessels. Later the changes take place in the vessel walls." "Degenerative changes also have been noted in the ciliary ganglion. The drug seems to have a selective action upon this part of the nervous system." In view of the fact that quinin is capable of producing a profound effect upon the nerve supply of the eye, it is difficult to determine whether the blindness following malaria is due to the malaria itself or to the quinin. The author has never seen a case of blindness following malaria whether treated with quinin or not.

Herpes labialis and also *herpes zoster* frequently occur in malaria, but it would probably be better to speak of them as symptoms or complications than as sequelæ.

Leukemia has been observed to follow malaria and has in some instances been thought to be caused by it. However, there are many cases of leukemia that certainly occur independently of malaria, and it is quite likely that in those cases following malaria the occurrence is simply a coincidence and that the leukemia is not a sequela.

Postmalarial anemia is frequently considered a sequela of the disease. It is true that the anemia sometimes lasts for many weeks or months and sometimes for a considerable time after the patient has been disinfected of malaria parasites. The anemia following attacks of malaria of moderate severity which has been properly treated rapidly clears up. However, in the chronic cases, and especially in those in which cachexia has developed, the restoration of the blood to normal is very slow. In such cases polychromatophilia and anisocytosis and stippling are often present for months after the patient has begun taking sufficiently large doses of quinin. Nucleated cells are also often present. In the author's opinion the longer the duration of chronic malaria, the longer the time required for complete restoration of the blood.

Cachexia is perhaps the most important sequela of malaria. It is not that it occurs so frequently, but that it is so important when it does occur. Acute cachexia can hardly be considered a sequela of malaria, but chronic cachexia, the usual form, is a sequela of chronic malaria. It is found where the severe forms of malaria are endemic and is almost always produced by estivo-autumnal infection. It is said to be much more common in the white race than in the negro, and also more frequent in males than in females. The following description of malarial cachexia is taken from Deaderick:[3]

"In this condition the parasites have obtained undisputed possession of the host. The defensive forces have been completely conquered, the blood-making organs can no longer meet the demands made upon them, and toxins, unopposed, work changes, often irreparable, in important organs. Cachexia has been classified as dry or humid, according to the absence or presence of anasarca, and as acute or chronic. Acute cachexia is characterized by a rapid onset and development of symptoms, and usually follows acute malaria, occasionally after only one or two attacks. These cases are infrequent. Chronic cachexia, the usual form, is a sequela of chronic malaria.

"Malarial cachexia is found where the severe forms of malaria are endemic. It may be stated as a general rule that the frequency of cachexia among the white race is an index of the prevalence of grave infections. It is much more common in the white race than in the negro. While negro children are not infrequently the subjects of malarial cachexia, it is much rarer in the adult negro. Of adults, males are more commonly cachectic than females; among children the proportion is about even. The condition rarely develops in persons of the better class, but is seen in those living under improper hygienic conditions, who neglect the treatment of acute malaria.

"Cases of cachexia developing without preceding malaria have been reported, but are subject to question. The malaria may have been unrecognized, as might happen with latent or masked infections. In regions where kala-azar is endemic it is only recently that this disease has been differentiated from malarial cachexia. Infections with the estivo-autumnal parasites are followed by cachexia much more frequently than tertian and quartan infections.

"The cachectic usually presents a singular appearance. The emaciated limbs are in marked contrast to the big belly, and the features are aged beyond the years. The most pronounced phenomena are the anemia and the enlarged spleen. The red blood-cells may be reduced to seven or eight hundred thousand per cu.mm. The leukocytes are generally normal in number or a little below. Numerous differential counts have shown a relative increase of the large mononuclear elements. The red cells may show basophil degeneration, polychromatophilia, poikilocytosis, and nuclei, but none of these changes are by any means constant. According to my experience parasites are rarely found in the peripheral blood. The spleen often extends to the umbilicus and to the crest of the ilium, sometimes beyond. It is usually hard and the anterior border presents a sharp edge. Pain and tenderness on pressure are not always felt. Occasionally a bruit is to be detected over the splenic area.

"The pulse is small, compressible, and may be irregular. Palpitation of the heart and hemorrhages, especially epistaxis, may occur. An anemic murmur over the precordia is often heard. Myocarditis and dilatation are not infrequent. The breath is short, sometimes amounting to actual dyspnea. A cough is common and signs of bronchitis may be elicited. Pulmonary edema is a late symptom.

"The temperature may be normal or subnormal for long periods, though evening rises are often observed. Typic paroxysms are not frequent. Fever often follows imprudences. Whether the fever of cachexia is due directly to parasitic activity or to organic changes is not definitely known. The appetite is generally poor and the digestion tardy. Epigastric pain, nausea, and vomiting may be complained of. The tongue and oral mucous membrane are pale. Diarrhea and dysentery frequently occur. Meteorism is common. The liver is usually somewhat enlarged at first; later it may become atrophic. Ascites is not a rare manifestation. When fever exists the urine is ordinarily scanty and highly colored. Delayed development of the genitals is common in the young and diminished sexual power is not rare in the adult. Indifference, intellectual torpor, somnolence, headache, and vertigo are observed in cachectics. Resistance to cold is lessened and rheumatic pains are experienced. The skin is pallid, dry, and rough, and may exhibit sores or purpuric spots. Anasarca may supervene."

Clinical Varieties.—Many clinical varieties, or types, of malaria have been described. The classification is usually based upon more or less arbitrary lines and in many instances serves but little purpose. The symptoms that may be produced in different individuals by malaria infection of one kind or another are frequently so greatly altered by individual circumstances or conditions that each variety or type may quickly change into another. The most useful purpose which this classification may serve is to indicate whether heroic treatment is urgent or whether the usual routine treatment is all that is necessary. Microscopic examination of the blood will determine this very much better than any clinical classification that can be made. This applies especially to the question of whether quinin should be given intravenously or whether the case justifies waiting for the somewhat slower action of the drug given by mouth. Although such a classification may not be of great service, it will probably be well for us to discuss briefly some of the varieties or types.

Malaria Infection without Recognizable Clinical Evidence of Its Presence.—If blood examination is made of all the individuals living in a community where malaria prevails, it is found that not only are malaria parasites found in those who have active malaria or who have had it during the few months previous, but that a good many others are infected who have not any recognized symptoms of the disease at the time of examination, and who have not had any for many months or years previous to the examination. Of the 6,664 persons found to be infected out of 31,459 examined in Bolivar County during 1916-17, 44.91 per cent. had no recognized symptoms and had not had any during the twelve months previous to the blood examination. There is a great deal more malaria of this variety or type than is generally supposed. It is true that many of such infected individuals may carry their infection latent and at some later date develop a more active type. At the same time, many others, perhaps the majority, finally lose their infection without even having active malaria.

Chills; Chills and Fever.—Paroxysms of intermittent malarial fever are nearly always ushered in by a chill. This is especially true with older people and less so with children. The younger the child, the less likely it is to have recognized chills. Children less than two years of age seldom have them. Tertian malaria is much more uniformly characterized by chills than either quartan or estivo-autumnal. Even tertian malaria, however, is not always accompanied by definite chills. In a region where there is a great deal of malaria many people speak of it as "the chills" and not as chills and fever. Although they always have fever following a chill, the fever is not as clearly recognized by laymen as the chill is. Chills, or chills and fever, do not occur in remittent malarial fever except perhaps at the beginning of the attack.

INTERMITTENT MALARIAL FEVER.—Intermittent fever may be of the quotidian, tertian or quartan type, paroxysms occurring every day, every second day or every third day respectively. Quotidian fever may be caused by two crops of either tertian or estivo-autumnal or by three crops of quartan parasites segmenting on alternate days. Tertian fever may be caused by one crop of either tertian or estivo-autumnal parasites. Quartan fever is caused by one crop of quartan parasites.

The fever lasts from an hour or two to several hours and may or may not be ushered in by a chill. The intermission in the quotidian type is usually considerably longer than the fever period. In the tertian type there is an intermission of more than one full day. In the quartan type there is an intermission of more than two full days.

REMITTENT FEVER.—Remittent malarial fever is not as frequent as was formerly supposed. At one time many other diseases, like typhoid, paratyphoid and other infections, were classified as malarial remittent fever. In fact, unfortunately too much of this confusion occurs even at the present time. The increased use of laboratory diagnosis, however, has very greatly reduced the frequency of this error. Remittent malarial fever does occur and may be produced by tertian, quartan or estivo-autumnal parasites. It is more likely to be produced by the estivo-autumnal, next by the quartan and least likely to be produced by the tertian form. The fact that the tendency of all malaria parasites to reproduce by crops is less marked in the case of estivo-autumnal malaria than in other varieties is supposed to explain the greater frequency of remittent fever in estivo-autumnal infection. Remittent fever is frequently called bilious remittent fever whenever there are gastro-intestinal symptoms accompanied by the vomiting of more or less bile.

ACUTE AND CHRONIC MALARIA.—To divide malaria into acute and chronic forms seems hardly necessary. Any case with acute clinical symptoms may be called acute. Those which remain infected but show few active symptoms may be called chronic cases. If there is sufficient reproduction of parasites to give rise to any considerable damage, such, for instance, as anemia, chronic enlarged spleen, or perhaps a moderately increased temperature, it would be especially appropriate to speak of such cases as chronic. There are many cases of this sort.

MALARIA RELAPSE.—Persons who have attacks of malaria and who do not undergo sufficient treatment to destroy the infection frequently have subsequent attacks from time to time, and these constitute malaria relapses. Approximately 50 per cent. of all the acute attacks of malaria that occur in a malarious region consist of malaria relapses and not of new infections.

BENIGN AND PERNICIOUS MALARIA.—Whenever malaria is not sufficiently severe to destroy or threaten to destroy the life of the patient, it is usually spoken of as benign, but whenever it reaches a stage of great severity, it is usually spoken of as pernicious malaria. There are certain clinical types which are especially included under this head —the comatose type, the eclamptic type, the algid type and sometimes the bilious remittent type. They are nearly always produced by estivo-autumnal parasites.

In the comatose type the patient has usually had several paroxysms, occurring in the course of recurring acute attacks or relapses, which have been improperly or insufficiently treated. Usually the patient is stricken rather suddenly with a severe paroxysm, perhaps ushered in by a chill, vomiting and rapidly developing unconsciousness. It may be mistaken for such conditions as apoplexy or sunstroke. The temperature is usually high, generally ranging between 103° and 106° F. (39.4° and 41.1° C.). There may be delirium for a time, giving way, however, to more or less complete coma. Unless prompt relief is obtained by the administration of quinin intravenously, death usually occurs. In other cases the patient may regain consciousness and go on to recovery.

The eclamptic type is found especially in children. The patient is seized with violent pains in the back of the head, vomiting and eclamptic seizures. Profound coma usually supervenes, accompanied by very high fever. If such a case is not examined early and prompt treatment instituted, death may occur within a few hours. Blood examination shows enormous numbers of parasites present.

In the algid type, there is profound prostration. The surface of the body is cold. A profuse, cold, clammy perspiration is present and the patient appears to be in a state of complete collapse. The temperature is not high, as a rule, and in many instances it is subnormal. Unless prompt relief by intravenous administration of quinin is afforded, death is likely to occur in a few hours. In many instances, the most heroic treatment fails to save the patient. Fortunately, it is not necessary that this type of the disease should develop. It occurs only in individuals who have had repeated recurrences and is therefore always due to neglect of proper treatment of previous infections.

In the bilious remittent type the patient is usually seized with uncontrollable vomiting and extreme prostration. Large quantities of bile are vomited and the fever usually runs a remittent but high course. Delirium or coma may supervene.

Treatment.—PROPHYLAXIS.—1. *General Prophylaxis.*—Under General Prophylaxis will be discussed those measures which may be applied in a given locality or area, large or small, for the purpose of preventing malaria among the entire people. These measures are directed either against the malaria parasites or against the transmitter of them. If we could entirely eliminate mosquitoes from any locality the transmission of malaria would at once cease. On the other hand, if we could destroy all the malaria parasites in a locality the transmission would cease, and not only would the transmission cease but there would be no more sickness from malaria. Malaria can be destroyed either in man or to some extent in the other host, mosquitoes.

(*a*) *Destruction of Malaria Parasites in Man.*—We may destroy the malaria parasites in the blood of a group of people either as the parasites are introduced into the blood or after infection and multiplication have taken place. The destruction of parasites by **quinin** immediately upon their introduction serves as a prophylactic measure so far as the individual is concerned and indirectly also as a prophylactic measure for the community. If we grant that proper doses of quinin taken at proper intervals will destroy malaria parasites as soon as they are injected into the blood by mosquitoes, we will also have to grant that if everybody in a given community would take quinin there would be no further transmission of the disease.

The most extensive use of quinin prophylaxis for all people in the community has perhaps been made by the Italians, and as a result there has been a great reduction in the prevalence of the disease. Many students of malaria may not appreciate the important part played by quinin prophylaxis in the campaign against malaria in Ismailia. The author certainly did not realize this until recently when reviewing the literature on the subject, especially an article in the Annals of Tropical Medicine and Parasitology by Stephens,[21] in which he gives more or less in detail the antimalaria measures carried out there by Ross, and the effects, resulting in the practical disappearance of malaria. So far as these details indicate, antilarval measures were not undertaken until after Major Ross' visit in September, 1902, and therefore could not have affected the prevalence of malaria before 1903. In February, 1902, the entire personnel of the canal company was put on systematic prophylactic quinin. It appears that only the workmen were required to take the quinin under supervision, but that it was optional with certain other employees. The number of cases of malaria fell from 476 in 1901 to 85 in 1902, due apparently entirely to the quinin prophylaxis. Stephens says: "To what the extraordinary fall of 2,591 in 1900 to 476 in 1901 is to be attributed is not clear. For although diagnoses made by the 'sisters' of the dispensary may not be accurate, yet if these 2,591 cases of 'fever' were not malaria, we are at a loss to what to ascribe them." . . . "It should be added that quinin at this time was given by the 'sisters' to those who came to ask for it, but to what extent it was given, what effect it had, it is impossible to say, unless one accepts these figures as affording the answer."

(*b*) *Quinin Prophylaxis for the Entire Population.*—A considerable amount of educational work is necessary in order to induce an entire population to take quinin prophylactically. In fact, it is only where malaria is very prevalent and people can be forcibly impressed with the importance of preventing it that they can be induced to take quinin for this purpose. It is one thing to persuade well people and those who have not had malaria and who, so far as they realize, are not likely to have it, to take quinin, and an entirely different thing to get those who already have malaria to take it for the purpose of disinfection. Where they are under suitable control, as for instance in the case of armies or groups of laborers, it may be practical to require all to take quinin, but with a free-living people who must first be convinced that they need it and whose coöperation must be secured by argument and publicity work, it is not to be expected that 100 per cent. of coöperation can be secured. Therefore 100 per cent. of prophylaxis could not be secured even if the remedy were perfect. There will be exceptional individuals who are antagonistic to any public move. There will be others who, on account of idiosyncrasy to quinin and on account of the discomfort it may produce in them, will fail to take it. There are still others who for various reasons may forget or neglect it.

The success of quinin prophylaxis with a large group of individuals will depend very largely upon the personal equation or upon the ability of those who undertake it to carry it out. There are many individuals who have little ability to secure the coöperation of the public in any move. There are others who would be able to obtain the confidence and coöperation of the same people. One who undertakes to carry out the administration of prophylactic quinin in a community should first be familiar with his subject. He should know what malaria is, and how it is carried from one individual to another, and he should also not have any doubt that the measures he is advocating will be successful if carried out.

House to house visits and personal contact with the people are very necessary. The visits must be made at frequent intervals in order that the objections that arise in the case of different individuals from time to time may be met and explained away. This close personal touch with the people is also necessary in order to correct any erroneous reports or impressions that would otherwise influence some individuals to discontinue their quinin treatment. In a group of people in a rural community in Arkansas to whom Derivaux[22] gave quinin either for prophylactic or sterilization purposes, only 17.64 per cent. took 100 per cent. of the treatment during the entire period. It is noteworthy, however, that 79.61 per cent. took over 50 per cent. of the quinin issued to them. It is very probable that in most instances, at least, those who took as much as 50 per cent. of their quinin would be disinfected or would be protected against malaria. This would therefore insure a high per cent. of protection. We must remember that in public health work it is not to be expected that 100 per cent. of results will be obtained except in special instances and when work is done on a limited scale. This is especially true where the success depends upon the coöperation of the people themselves.

The follow-up work in communities Nos. 24 and 25 in the author's observations in Bolivar County showed that by repeated visits and by keeping in close touch with the people, about 85 per cent. can be induced to take sufficient quinin to insure protection There will be some individuals in every large group who will refuse to take quinin, no matter who works with them, and regardless of almost any other circumstances which may exist.

Quinin prophylaxis depends upon the coöperation of the people. As a matter of fact, success or failure depends not so much upon what quinin will do, as upon whether the coöperation of the people can be secured to a sufficient extent to induce them to take enough of the drug to obtain the desired results. The writer believes that there is no question in the minds of those who are informed on the subject that if people will take quinin the transmission of malaria can be prevented. The practicability of quinin prophylaxis in rural communities or in different groups of people in different localities and different parts of the world depends very largely upon coöperation. Among those people who, on account of lack of information or of prejudice against the use of quinin or for some other reason, are not inclined to take the drug, quinin prophylaxis is impractical. On the other hand, among people who have sufficient intelligence to coöperate and to appreciate the movement, quinin prophylaxis will be successful in the hands of intelligent and competent workers.

(*c*) *Control of Malaria by Disinfection of Malaria Carriers.*—Usually, whenever we speak of quinin prophylaxis we think of taking quinin to prevent infection. There is, however, a more practical and successful method of preventing the spread of malaria by the use of quinin than the one just described. That is, disinfecting infected persons. If we could disinfect every malaria carrier in a given locality so that there were no malaria parasites present, there naturally could be no further transmission of malaria in the community because there would be no malaria parasites to transmit, regardless of the number of mosquitoes that might be present. It is true that new cases might be introduced as a source of infection, but transmission from the new cases would be very slow, and if we could ever carry out antimalaria work by disinfecting malaria carriers with quinin to a sufficient extent to eliminate or practically eliminate the disease, any new cases that occur would naturally receive proper and prompt treatment so as to destroy the parasites and prevent any considerable spread of the infection. In fact, the author believes that if the disease can be eliminated or practically eliminated from a country, no matter how malarious it is, by the general use of quinin for the disinfection of all infected persons, there need be no concern as to the subsequent spread of the disease. The population will have been so well informed and so convinced of the importance of quinin treatment by the experience and object lesson that any tendency to recrudescence will take care of itself. Relapses may occasionally occur in individuals who take proper treatment, but if almost all the people in the community take quinin in proper form to disinfect themselves whenever they have malaria, there can be no spread of any consequence.

(*d*) *Locating Infected Persons in a Community.*—In order to locate all malaria carriers in a community, a malaria survey must be made, and this must include, of course, everybody in the community. This survey should ascertain the history of recent attacks of malaria and should also include blood examinations of all who give negative histories. By the studies in Bolivar and Sunflower Counties it was found that in that region, which is supposed to be representative of the malaria section of the Southern States, at least 50 per cent. of all the attacks of malaria that occurred during a year were relapses from previous infections and that not more than 50 per cent. represented new infections. It was also found that people who had attacks of malaria during a given year were most likely to have attacks during the next year (these were, of course, largely relapses) and also that they were most likely to be malaria carriers. Some of them were found upon examination not to have malaria parasites at all times. It was decided, however, that they should all be considered as malaria carriers or as probable malaria carriers and that unless they had had proper treatment, which seldom occurred, they should be given the necessary disinfecting treatment.

All persons who have had an attack of malaria during the twelve months preceding examination should be treated. Usually there is not the slightest difficulty in inducing them to take quinin and to take it properly. As a rule they know they have had malaria, and are willing to take the proper treatment to get rid of it. Many of them think they still have it in their systems and are willing to take the proper treatment in order to eliminate it.

Of those who give negative histories it is desirable to make a proper blood examination. As has been pointed out under Diagnosis, blood examination does not find 100 per cent. of the infected people in a group, but it does find a large per cent. of them and especially those who have sufficient parasites to be a source of infection at the particular time. In the vast majority of cases the person who gives a negative history and also a negative blood examination, is either not infected at all or has sufficient resistance to throw off the infection without treatment. This is not always true, of course, but the tendency is in this direction, at least. Therefore, those who are carrying infection but who are overlooked by both the history and the blood examination are few in number and are least likely to be a source of spread of malaria later.

Both those who give positive histories and those who are found positive on blood examination should be given the quinin treatment necessary to disinfect them. Just what this treatment is and the reasons for the exact details will be dealt with more extensively under the head of Medicinal Treatment, but it consists of 10 grains (0.65 grams) of quinin daily for adults and a proportionate dose for children, for a period of eight weeks. The treatment disinfects more than 90 per cent. of those who take it.

(*e*) *Necessity of Issuing the Full Eight Weeks' Treatment at One Time.*—It is much better to issue the full eight weeks' treatment at one time than it is to issue it in divided quantities. In the Mississippi Delta work the method was adopted of issuing bottles of 112 tablets to those who take tablets and eight ounce bottles of syrup of yerba santa containing the necessary amount of quinin to those who take syrup. It is best to explain to the patient at once that it is necessary for him to take the entire treatment in order to be sure of eliminating the infection. If the entire treatment is not furnished at one time, it may happen that for some reason or other the part that is furnished will give out before the balance is supplied. Perhaps the most important reason for giving the full treatment at one time is to impress the patient that this is the minimum that is required to disinfect him, and to create the general impression among the people that in the future malaria must be treated by a full eight weeks' treatment if disinfection is to be accomplished. Perhaps the greatest drawback to disinfection has been the insufficiency of the treatment employed. The treatment ordinarily prescribed by doctors does not disinfect the patient, largely because there is no definite fixed duration of treatment impressed upon the patient at the outset as being necessary. Many doctors simply prescribe sufficient treatment for a few days, and even although they intend to repeat or continue the treatment they fail to impress the patient with the absolute necessity for continuing it for a sufficient length of time. The patient feels well in a few days and does not see the necessity of taking quinin any longer and therefore, of course, discontinues it. On the other hand, if we issue the full treatment at once and at the time of furnishing it explain to the patient carefully and thoroughly that nothing short of the full eight weeks' treatment is likely to be successful, we impress him and we are much more likely to have his coöperation.

(*f*) *Intermittent versus Daily Quinin Treatment for Disinfecting Malaria Carriers.*—The advantages of the daily administration of quinin over intermittent treatment is discussed in detail on page 630. There are sufficient advantages in favor of it so that there is, in the author's judgment, no question whatever that it is the proper treatment. It must be granted that if intermittent treatment is continued sufficiently long it may prevent relapses during the period of administration, but the author is quite convinced that the daily quinin treatment is much more efficient in disinfecting infected persons. He has come to this conclusion after considerable research and investigation and with reluctancy, after having once held the opposite view. At that time, however, his opinion was based more upon theoretical grounds than upon actual observation and research.

In the ninth of a remarkable series of studies in the treatment of malaria recently published in the Annals of Tropical Medicine and Parasitology by Stephens and others,[23] the authors present experimental evidence which they conclude indicates that interrupted treatment is more efficient than continuous treatment. They compared the effect of 30 grains (1.95 grams) of quinin daily with that of 30 grains (1.95 grams) on two consecutive days weekly for a period of eight weeks, and also that of 45 grains (2.925 grams) daily with that of 45 grains (2.925 grams) on two consecutive days weekly for eight weeks. The number of cases was small, but their conclusions were that interrupted treatment gave by far the best results. There are so many unusual and unexpected conclusions in this series of experiments that the author feels himself obliged to await further confirmation before advocating their general adoption. He confesses that the experience of these writers with malaria relapse has been so different from his own observations and those of others with whom he has talked that he feels that it is best to withhold judgment until the results are confirmed by other investigators. Even though it may be possible that 45 grains (2.925 grams) of quinin on two successive days are effective in preventing malaria, it is very certain that this amount of quinin cannot be given to infected people in a community to a sufficient extent to result in any great amount of malaria control. People who are up and about cannot take 45 grains (2.925 grams) of quinin a day without a great deal of discomfort. Many laborers cannot work in fields or elsewhere while they are under the influence of this amount of quinin. On the other hand, almost any person can continue work while under the influence of 10 grains (0.65 gram) of quinin.

A very important advantage that the daily administration of quinin has over the intermittent is that the treatment is less likely to be forgotten and neglected. Those who take a dose of quinin every night before retiring soon establish the habit of taking it and are less likely to forget and to neglect it than those who try to take it on one or two days a week.

(*g*) *The Extent of Malaria Control That Can Be Accomplished by Disinfecting Infected Persons.*—In the experimental treatment of the infected among 31,459 persons in Bolivar County during the years 1916 and 1917, there appeared a reduction, as indicated by reëxamination of the blood, of 35.52 per cent. This includes all of the experimental groups, some of whom were treated in a manner that, it is now known, could not have greatly reduced their malaria. In one community in which a reëxamination was made exactly twelve months from the time the first examination was made and treatment was furnished, the second examination showed a reduction of 83.32 per cent. in the amount of infection. In Sunflower County during 1918 this method of malaria control by disinfecting malaria carriers was carried out under more ideal conditions and more as a demonstration than as an experiment. In the second community examined, in which 432 were surveyed and treated in 1918, a resurvey in 1919, exactly twelve months from the previous one, shows a reduction of 95 per cent. in the prevalence of malaria during the twelve months following the treatment as compared with the preceding twelve months. This is based upon the histories of attacks of malaria. The work here shows that it is possible to prevent the transmission of malaria in a given locality or area by disinfecting infected persons, and also that it is possible to induce the class of people living in the Mississippi Delta region to take the necessary quinin to disinfect themselves.

(*h*) *General Mosquito Control Measures.*—Mosquitoes are to be controlled almost entirely by preventing the development of larvæ, or by what would properly be called antilarval measures.

(1) *Elimination of Breeding-places.*—Mosquitoes spend the larval stage in water. If there is no water suitable for *Anopheles* to breed in, there is no development of *Anopheles* larvæ. *Anopheles* breeding-places can be eliminated either by **filling** so that water does not stand at all, or by **drainage.** Artificial containers sometimes serve as breeding-places and should therefore receive attention. The drainage of mosquito breeding-places will depend very largely upon the particular locality. The most practical method of draining should be followed in each instance. Generally speaking, either filling or permanent drainage construction is to be recommended. Temporary work soon loses its effectiveness unless constantly cared for, whereas permanent work, especially filling, when once properly done requires no further attention.

(2) *Oiling and Poisoning.*—In those collections of water that cannot be filled or drained, oiling may be resorted to. It should always be done with the knowledge that it is a temporary measure. The best method of applying oil is by means of sawdust saturated in the oil. Usually a mixture of about equal parts of crude **petroleum oil** and **kerosene** is most satisfactory. Sawdust soaked in this way may be carried by means of buckets or other containers and scattered, especially at the edges of breeding pools. The sawdust continues to set the oil free for some time after it is put into the water and it is a much more satisfactory method of ensuring a proper spread than the spray pump or other means. To be of service the film of oil must entirely cover the area in which the larvæ are to be killed. It kills them by suffocation. They are not able to project their breathing tubes through the thin film of oil on the water.

Poisoning by means of different larvacides and sometimes by waste from manufacturing establishments like, for instance, **niter cake,** is also successful. It is very limited in its application, however, because of the danger of poisoning animals and possibly human beings. Another serious objection to any other kind of poisoning is that it kills the predatory insects and also the fish which destroy larvæ. As long as the water remains poisoned, it of course makes little difference if all fish and predatory insects are killed, but as soon as it is replaced by fresh water, or when the poison in the water is removed or neutralized, there is a more favorable breeding-place than ever. Pools of water that can be **stocked with fish** may be kept free of larvæ in this way. The pool must be kept **clear of floatage,** trash and débris and also of weeds, if the fish are to destroy the larvæ.

Collections of water that cannot be drained or oiled effectively can be kept free of larvæ by thoroughly and frequently cleaning them of débris and floatage and also by keeping the banks perfectly clean.

(3) *Clearing.*—*Anopheles* larvæ breed most freely in collections of water that are more or less covered by vegetation such as grass, weeds, trees, etc. Not only are such collections more suitable for breeding, but the adult mosquitoes are protected from their enemies by the vegetation. **Clearing the land of vegetation,** especially of trees, is a very important factor in the control of *Anopheles.* In a large part of the ma-

laria section of this country there are many bayous, ponds and streams in which mosquitoes breed in large numbers. These are usually uncleared. The custom is to clear the high ground for cultivation or other developments but to leave the low ground of these places uncleared. *Anopheles* come out from such swamps or weeds to attack their victims and then return to the swamp for protection and also to breed. A very important factor in malaria control is clearing and then pasturing the land bordering the bayous, lakes and streams. Usually it makes excellent pasturage. The author believes that he can say with perfect confidence that if the bayous and streams of Sunflower County, one of the heavily infected counties of the Mississippi Delta, were all cleared and well pastured, malaria would practically disappear from the country and a considerable profit would also result from the use of these pastures.

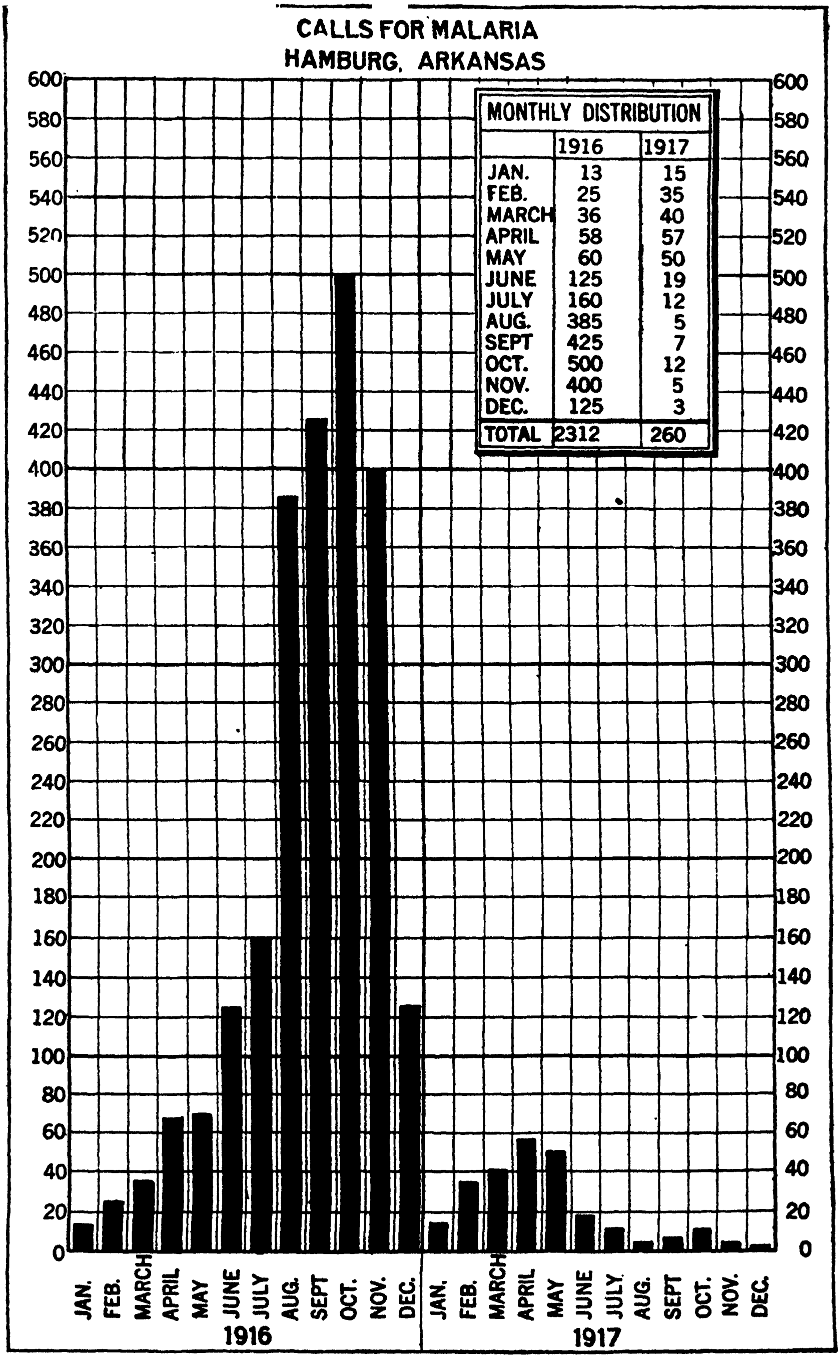
During the past few years a number of demonstrations in malaria control by antimosquito measures have been made by the United States Public Health Service and by others. A recent report of malaria control at Hamburg, Arkansas, by Taylor[24] is illustrative of what can be done by a concentrated effort in mosquito control. In this instance no major operations were undertaken or necessary. Proper draining of ditches, filling of unnecessary pools, etc., were carried out. The results of the work are strikingly shown in the accompanying chart (Fig. 16). The per capita cost of this work was $1.45.

The most extensive malaria control work ever carried out has recently been done by the United States Public Health Service in the extracantonment zones in fifteen different states in the United States. LePrince[25] stated that the entire area in which *Anopheles* control had been accomplished was over twelve hundred square miles. "Where cantonments have been located in notoriously malarious sections very little malaria has been contracted by enlisted men, and the malaria sick rate among enlisted men in camp has been very much lower than it would have been had they stayed at home. The commanding medical officers at the cantonments report mosquitoes as being scarce at nearly all camps, and *Anopheles* as being seldom seen, except at two of the aviation camps near rice field areas." The cost of drainage, oiling, supervision, equipment and transportation averaged about $1.80 per acre of territory controlled.

There is no longer any question as to whether malaria can be controlled in this way. The question is whether people desire to do it. With sufficient funds and the desire, there is nothing to prevent practical elimination of *Anopheles* and incidentally of malaria from almost any locality.

2. *Individual Prophylaxis.*—An individual may protect himself against malaria infection either by not allowing the parasites to be introduced into his blood or by killing them as they are introduced.

Protection against infection may be summarized as protection against the bites of infected mosquitoes. An individual's chief interest should be to **avoid being bitten by mosquitoes** that may be infected, but he



MONTHLY DISTRIBUTION

	1916	1917
JAN.	13	15
FEB.	25	35
MARCH	36	40
APRIL	58	57
MAY	60	50
JUNE	125	19
JULY	160	12
AUG.	385	5
SEPT	425	7
OCT.	500	12
NOV.	400	5
DEC.	125	3
TOTAL	2312	260

Fig. 16.—Calls for Malaria, 1916 (estimated) and 1917, Hamburg, Arkansas. Population 1,285. Office, hospital and residence calls included (Taylor, Southern Medical Journal).

may also indirectly, for his own protection, control the number of infected mosquitoes that are in his immediate surroundings. For instance, if an individual is a member of a family or of a household or group of people among whom there are one or more persons who have malaria, he can contribute very largely to his own protection by influencing those who are infected to disinfect themselves. This will be explained more in detail in another part of this article. The malaria-bearing mosquitoes that become infected in a given house tend to return to the same house and to infect others there instead of going to other buildings. Therefore, whenever one is living with a group of people, in a malarious section, he should exert any influence he has to induce every person who has malaria to take proper **quinin treatment.** A man who is familiar with the treatment necessary to disinfect infected persons and can impress others with its necessity has a valuable means of reducing the danger of infection to himself.

In addition to this, he should also encourage in any way that he can the proper protection of known malaria carriers from mosquito bites until they are disinfected. It is of great importance that malaria carriers in a given group of people should be protected against mosquito bites. Since the *Anopheles* feed especially at night, the chief protection needed is during the night. Sleeping in well screened rooms and also under well arranged **mosquito nets** becomes therefore of great importance. The length of time that a malaria carrier. is likely to remain a potential source of infection while taking proper treatment varies very greatly in different individuals. In the majority of cases of simple tertian infection the gametes disappear from the peripheral blood very quickly, so that they would not be a source of infection to mosquitoes. Even 10 grains (0.65 grams) of quinin daily usually cause them to disappear in two or three days. The gametes of quartan malaria are very little more resistant to quinin. On the other hand, the crescents of estivo-autumnal infection are frequently present in sufficient numbers to produce mosquito infection for at least two or three weeks, although in a majority of instances they disappear in a few days. Since we have no way of knowing who the exceptional cases will be and since in many instances it is not known which variety of parasites is present, the safest thing is for all persons known to be infected with malaria to be especially protected from mosquito bites for a period of at least two or three weeks.

In at least three cases Darling[26] observed the presence of crescents in sufficient numbers to produce infection while the patients were taking two grains (0.65 gram) of quinin t.i.d. for a period of twelve days or more.

Protecting oneself against the bites of mosquitoes is more direct and effective personal prophylaxis. In intensive malarious sections it is almost impossible to so thoroughly screen out mosquitoes from residences as to furnish absolute protection. Unless, however, *Anopheles* are very abundant and there is a great deal of malaria present in a locality, one may protect himself by staying in well-screened houses during the

Anopheles biting time. Although under exceptional circumstances *Anopheles* will bite during the day, they bite so much less frequently then than they do at night that practically all the transmission of malaria takes place at night and there is extremely little danger during the daytime. One should protect oneself from sunset to sunrise and need not fear infection during the day. Not only is it necessary to have the living and sleeping quarters well screened, but one must avoid going out, especially to other residences and to other places where infected people have been and where there are likely to be infected mosquitoes present. Public gatherings at night are especially likely to be a source of infection. To protect one's self, it is necessary to keep one's quarters well screened and to stay behind the screens during the proper hours. Whenever an individual deviates from this rule, he reduces his chances of avoiding infection to a corresponding extent.

Individuals may protect themselves to a greater or lesser extent by sleeping under well arranged and efficient mosquito nets, even though they are obliged to sleep in houses or camps in which there are infected mosquitoes. A large part of the infection with malaria takes place while the victim is asleep. Bed nets should be used in all instances where the screening of the house is not thorough and well maintained.

Quinin Prophylaxis.—There has been great difference of opinion expressed as to the value of quinin prophylaxis. Many observers have obtained almost 100 per cent. of efficiency from this means alone, whereas others have claimed to observe frequent failure or poor results from quinin. The best information that the author can obtain from reading the literature on the subject is that in the vast majority of cases where results have been unsatisfactory or imperfect, the fault has lain chiefly with the method of prophylactic treatment. Frequently, also, the statements of unsatisfactory results are made without care and accuracy. It often occurs that an observer states that he gave quinin to everybody in a given group of people and that in spite of this much malaria developed. Upon further reading it is often found that the dose employed was insufficient or that the treatment was not systematically administered. In a community where a large part of all the population are infected with malaria, quinin prophylaxis would certainly not be successful to the same extent as it would where there is less malaria. Just as soon as an individual stops taking quinin for a few days he is just as susceptible to infection as if no quinin had ever been taken.

Quinin destroys the malaria parasites whenever they are introduced into the blood, provided only the drug is present in the blood at the time they are introduced or soon thereafter in sufficient concentration. Since exposure occurs every day, a person is likely to be infected any day. In order to kill the parasites before they have had time to develop and multiply it is necessary to have sufficient quinin in the blood at all times to kill parasites. If, for instance, an individual takes quinin to-day, after a couple of days the dose taken has been eliminated, and he can be infected by the bites of infected mosquitoes just the same as if he had not taken any quinin at all. If he should wait several days before taking another dose of quinin, any infection that took place in the interim between the days on which he took quinin and had sufficient in his blood to destroy the parasites, would result not only in infection, but in a multiplication of the parasites. They would multiply and become established in those tissues and parts of the body in which parasites are more or less protected from the action of quinin. The taking of quinin at intervals of several days, therefore, could certainly not lead to the same protection as taking quinin daily would. And yet intermittent administration has been advised by a great many authorities on the subject. The method of large doses given at considerable intervals was canonized by Koch. His method consisted in giving 16 grains (1.040 grams) of quinin daily every ninth and tenth day or every eighth and ninth day, or even every seventh and eighth day if malaria be very prevalent. There have been various modifications of this method.

The Italian method of administering quinin for prophylaxis is by daily doses and Celli[27] gives the following table of the results of its general use in this way, showing the reduction in the cases of malaria in the Italian army:

Table 5.—Results of Quinin Prophylaxis in the Italian Army. (*Celli.*)

Year	Number of men	Attack Rate	Recidivates	Primitives	Observations
		Per cent.	Per cent.	Per cent.	
1902	199,253	27.44	21.41	6.03	
1903	206,468	24.14	17.85	6.28	Begun quinin prophylaxis.
1904	210,637	19.21	12.71	6.50	Continued quinin prophylaxis.
1905*	218,409	21.52	13.04	8.48	Do.
1906	211,245	18.99	12.67	6.32	Quinin prophylaxis extended.
1907	202,320	12.46	7.96	4.50	Do.
1908	216,679	8.04	5.19	2.85	Do.
1909	228,951	6.96	4.72	2.24	Do.
1910	234,104	5.10	3.23	1.87	Do.
1911	233,517	4.90	3.04	1.86	Do.

* Year of periodical recrudescence of the epidemic.

The reduction of malaria as a result of this quinin prophylaxis is shown on the following page in Table 6, which gives the new cases in the hospital of Taranto.

The author regrets that he is not able to obtain the data to bring these tables up to date. The evidence, however, is sufficient to show conclusively that quinin prophylaxis has a great effect in reducing the prevalence of malaria in a group of people, and therefore that it has a similar effect in preventing the disease in individuals.

In the Bolivar County experiments all the people living in each of two communities, containing a total of 1,657 people, were subjected to

Table 6.—Results of Quinin Prophylaxis in the Hospital of Taranto.

Year	New Cases		Observations
	Total	Per cent. of men	
1900	193	20.19	
1901	130	13.19	
1902	35	14.64	
1903	81	8.33	Begun quinin prophylaxis.
1904	89	9.65	Do.
1905*	107	10.09	General quinin prophylaxis.
1906	72	7.00	Do.
1907	74	6.75	Do.
1908	46	3.94	Do.
1909	23	1.25	Do.
1910	13	.75	Do.
1911	21	.96	Do.

*Year of periodical recrudescence of the epidemic.

daily quinin prophylaxis. The dose was 5 grains (0.324 gram) for adults and ¼ grain (0.016 gram) for each year of age for children. This was kept up for from three to five months. During that period there was great reduction in the prevalence of malaria, but a number of cases of malaria occurred in persons who had previously had attacks. The author was quite convinced that the dose employed, namely 5 grains (0.324 gram) a day, was not sufficient to prevent recurrences in every instance, i.e., not sufficient to prevent recurrences of attacks in some of the malaria carriers. The author's opinion now is that the dose of quinin necessary to protect against malaria infection is exactly that necessary to disinfect an individual after clinical symptoms have been relieved by treatment, that is, 10 grains (0.65 gram) for adults and corresponding doses for children. He does not believe that there should be any difference made between the dose taken to prevent infection and that taken to disinfect infected individuals. Therefore the author's opinion is that by taking 10 grains (0.65 gram) of quinin daily an individual may obtain almost absolute protection as long as treatment is continued. This dose should be taken at night before retiring, as in the treatment for disinfection of carriers. The proportionate dose for children is as follows: under one year, ½ grain (0.0324 gram); one year, 1 grain (0.065 gram); two years, 2 grains (0.13 gram); three and four years, 3 grains (0.195 gram); five, six and seven years, 4 grains (0.260 gram); eight, nine and ten years, 6 grains (0.40 gram); eleven, twelve, thirteen and fourteen years, 8 grains (0.52 gram); fifteen years or older, 10 grains (0.65 gram). The form is exactly the same as that used to disinfect infected persons: that is, **tablets** for those taking 6, 8 and 10 grain doses and quinin suspended in **aromatic syrup of yerba santa** for those taking ½, 1, 2, 3 and 4 grain doses.

Possible Harmful Effect of Long-continued Taking of Quinin.—In many instances quinin has been kept up for several months, and when it is given in small doses of 10 or 20 grains (0.65 or 1.30 grams) a day no untoward effects have been observed. Bates[28] cites a case in which a patient who was accidentally overlooked took 30 grains (1.95 grams) of quinin a day for a period of seven months, in which time no ill effects could be noticed. The patient stated that "he had long since ceased to be troubled by ringing in the ears or other unpleasant symptoms." Bates states that it was not uncommon for patients to take 30 grains (1.95 grams) of quinin a day for two or three months and that in these cases no apparent ill effect from the drug was observed. In the light of the many and almost uniformly favorable reports in the literature that quinin in reasonable doses is practically never harmful, and in view of the author's own observation and experience, he has no hesitancy in advising the use of 10 grains (0.65 gram) of quinin daily for months or even for years as a prophylactic against malaria, whenever necessary. Not only is this advice given, but the further counsel is added that barring extremely rare exceptions it will prove efficient, and that one who is obliged to do so may travel and live in malarious regions without danger if he will simply take the proper amount of quinin. Not only is this so, but in those instances where it is necessary to send armies or groups of laborers or others into malarious regions for different purposes, it is perfectly practicable and feasible to prevent the havoc that would otherwise be wrought by malaria by systematically giving quinin. Any individual who cares to protect himself may do so in this way.

GENERAL MANAGEMENT.—The general management of cases of malarial fever is not different from the management of other fevers. The patient should be **put to bed** and should remain in bed for from forty-eight to seventy-two hours. In the pernicious cases, of course, the period in bed should be longer than this. The **bowels** should be **emptied,** preferably with a **purgative,** although **enemata** may serve the purpose. In all severe cases, especially in children, it is of great importance at first to wash out the bowels and also to give a purgative as soon as it can be done. Some believe that simple **saline purgatives** are as good as any, but others strongly advocate the use of **calomel.** In the author's judgment, in every case in which the diagnosis of malaria is reasonably certain, calomel should be given, followed in a few hours by the saline. There is every reason for the belief that calomel is superior to any other purgative in malaria. Although the author strongly advocates the use of a purgative, calomel by preference, at the beginning of all cases of acute malaria, he wishes to be clearly understood as opposing any delay in the administration of the specific drug, **quinin,** while waiting for the action of calomel or other medicine. Quinin is always to be begun in malaria as soon as the diagnosis is made, and it can be given. The serious mistake is often made of giving calomel or some other purgative and waiting for it to act before starting the quinin. This is not only a serious mistake, but in the case of pernicious malaria, it may frequently result in the death of a patient who could otherwise have been saved. An instruction frequently given by physicians who visit malaria patients is to give a purgative, wait until it acts and then begin quinin. If, for some reason or other, the purgative is slow to act there may be a delay of several hours or even of a day or two before the patient is given the life-saving specific remedy, all this time having been lost in waiting for the action of other drugs that have no specific action.

After the acute attack of malaria has passed and the temperature has returned to normal, the patient may be allowed to get out of bed and, as soon as he is strong enough, to resume his usual occupation. It is not necessary to keep patients in a hospital or at rest while convalescing from malaria, except of course following severe or pernicious attacks. In such instances the condition of the patient will indicate when he is able to resume work. The important thing is to give proper instruction as to quinin treatment before discharging the patient from the hospital, or allowing him to leave his bed.

It is very important that all malaria patients should sleep in well-screened houses or under suitable bed nets, or both, in order to keep out mosquitoes.

DIET.—In acute malaria the first thing to do is to empty the alimentary canal and at the same time administer quinin. The second important thing is to **avoid a heavy diet** of any kind. Generally the diet should consist of liquids for a day or two, or even longer in pernicious cases. During convalescence and the period of treatment necessary for disinfection, the patient should have the usual diet but should avoid overeating and especially refrain from eating large quantities of indigestible food. In regions where malaria is very prevalent, there is a common belief that such things as muscadines, unripe watermelons and green fruit will cause chills and fever. They do not actually cause chills and fever, but they do precipitate attacks in people who are already infected. They favor the development of malaria parasites and the production of clinical attacks and should therefore always be avoided by those who are known to be infected.

CLIMATOLOGY.—A climate which favors the production of *Anopheles* mosquitoes favors the spread of malaria. Great variation in the temperature, especially if changes are sudden, tends to produce attacks in people who are already infected. Sudden chilling of the surface of the body by getting wet while hot, etc., tends to produce attacks in those who are already infected and to make the disease worse in those who are having clinical symptoms. Regardless of these facts, it is not necessary for any person to leave a malarious country in order to get rid of malaria infection nor to go to a high, dry climate to recover from malaria. Given proper specific treatment, one should be able to recover from malaria in the most intensely malarious spot in the world.

Climate, or at least elevation, seems to have some effect upon the development of clinical symptoms and upon recovery from an attack. It frequently occurs that persons who have gone for months and perhaps for years without having attacks while living in a low, warm, malarious region soon develop a chill or an acute attack of malaria when they go to a higher altitude. Usually, also, the chill that occurs under these circumstances is more severe than previous ones have been. A few days of treatment give prompt relief, and it is noteworthy that many such persons lose their infection without continuing treatment for any great length of time. Although as indicated a moment ago, resort to special localities and climate is not necessary in any case, it is a fact that patients are usually cured of their malaria more rapidly in high altitudes than in lower ones.

LOCAL TREATMENT.—There is no local treatment indicated for malaria except perhaps for the chronic enlarged spleen of long duration, in which counter-irritation by means of **red iodid of mercury ointment** has been recommended. The author is frankly of the opinion that experimenting with such methods tends to cause neglect of the specific remedy, and that it should perhaps never be resorted to. There is great doubt whether it has any efficiency whatever.

TREATMENT OF SYMPTOMS.—The fever is sometimes sufficiently high, 104° to 106½° F. (40° to 41.4° C.), and the headache and suffering so great as to justify and demand treatment to relieve them. The **coal tar preparations** are useful, and although there is considerable objection raised to their use, the harm or possible harm is certainly overbalanced by the relief they afford the patient. It is not necessary that large or objectionable doses should be given.

The nausea and vomiting that occur with acute attacks of malaria are best relieved by **calomel.** In the pernicious cases, especially in those of children who have convulsions, **reducing the temperature** by baths and cold enemata is indicated.

SPECIFIC THERAPY (VACCINES AND SERUMS).—There is no excuse nor scientific basis for using or trying to use vaccines or serums in the treatment of malaria.

MEDICINAL TREATMENT: DRUGS.—Malaria is one of the diseases for which we possess a specific. All that is required to obtain 100 per cent. of results is the proper use of **quinin.** Barring moribund cases or those in which too much damage has already been done, there are practically no exceptions. There are as many methods of treating malaria as there are authors who have written on the subject. No endeavor will be made here to describe the methods that have been advocated by different authorities, but the author will give what in his judgment is the most practical and correct treatment, based upon a study of the treatment advised by different authorities and also upon rather wide experience and opportunity for observation.

(1) *Dosage.*—The dose of quinin used in the treatment of malaria should be sufficient to kill the malaria parasites in the blood without injuring the patient. There are parasites lodged in the organs and tissues of the body which are entirely out of reach of quinin for the time being, no matter how large the dose may be. All that we can hope for is to kill the parasites that are in the free circulating blood, and we can really only hope to kill the asexual parasites at that. Ten grains (0.65 gram) of quinin are sufficient to destroy the parasites that are present in the blood during the time that the maximum concentration of quinin is present. Five grains (0.324 gram) are not sufficient. Much larger doses than 10 grains are no more efficient. The larger the dose of

quinin, the more discomfort produced. Some people can take 30 or 40 grains (1.95 or 2.60 grams) of quinin during a day without great discomfort and some can even take as much as 90 or 100 grains (5.85 or 6.50 grams). Few people are made very uncomfortable by 10, 20 or 30 grains of quinin per day, especially while they are in bed or at rest. The author's own feeling is that 10 grains of quinin is the proper dose for adults and that it should be repeated as often as necessary to obtain the proper amount of quinin during a twenty-four hour period. He does not believe that 10 grains should be exceeded at any time. This is especially true of intravenous administration, as well as of administration by mouth. If there is ever any reason for the use of quinin intramuscularly, the dose should not exceed 10 grains. It may be repeated as frequently as is necessary to administer the required quantity.

(*a*) *Proportionate Dose for Children.*—It is usually said that children can take quinin better than adults and that they should have proportionately larger doses. In a large series of experimental treatments of malaria to disinfect malaria carriers in our Bolivar County work we gave ½ grain (0.0324 gram) for each year of age up to twenty years and then the 10 grain (0.65 gram) dose. An analysis of results from this treatment showed that there had not been the same proportion of disinfection in children as in adults. From the data in hand we were able to calculate what dose would be required to disinfect as large a per cent. of children as were disinfected by 10 grains in adults. That is as follows: under one year, ½ grain (0.0324 gram); one year, 1 grain (0.065 gram); two years, 2 grains (0.13 gram); three and four years, 3 grains (0.195 gram); five, six and seven years, 4 grains (0.260 gram); eight, nine, and ten years, 6 grains (0.40 gram); eleven, twelve, thirteen and fourteen years, 8 grains (0.52 gram); fifteen years or older, 10 grains (0.65 gram).

(2) *Mode of Administration.*—Barring pernicious cases in which there is reason to believe that the patient's life depends upon getting quinin into the blood stream at the very earliest possible moment, quinin should always be given by mouth. It is slowly absorbed, the maximum quantity reaching the blood stream in about eighteen hours, but a considerable concentration is present in two hours after its administration.

In pernicious cases where it is thought necessary that the quinin should reach the blood stream at once, intravenous administration may be a life-saving measure. In that instance, not exceeding 10 grains of bimuriate of quinin dissolved in not less than 20 c.c. of normal salt solution should be administered at once. A large, all glass syringe is the proper apparatus for this purpose. One who is competent can give the injection in this way almost as easily as hypodermically. Intravenous administration of any drug, especially quinin, is quite a formidable procedure and should never be resorted to except where it is absolutely demanded. There is no excuse for the administration of quinin intravenously for the routine treatment of ordinary malaria, and the use of this method for this purpose can only be condemned.

(3) *Time of Administration.*—Different authors have advocated the

administration of quinin at certain times, with special reference to the occurrence of chills. The advice is wrong. The time to begin administering quinin for malaria is promptly after the diagnosis has been made. As soon as the physician knows that he is dealing with a case of malaria nothing should prevent beginning the use of quinin at once. He should not wait for the action of a purgative, nor for the fever to go down. He should not wait for a certain time preceding the next paroxysm, but should begin quinin at once. In treating acute attacks of malaria about one dose every eight hours should be given for the first three or four days without regard to anything except the object of administering the desired amount during the twenty-four hour period. Thirty grains (1.95 grams) during twenty-four hours is sufficient for all cases, barring perhaps extremely rare pernicious cases. In pernicious cases it is proper to give a dose of quinin intravenously and to repeat the dose every two or three hours until 30 grains have been administered. Not a single dose, however, should be given intravenously after the patient is able to take quinin by mouth. In the most severe pernicious cases not more than two or three doses should be given intravenously at the short intervals of two or three hours. After that it should certainly not be repeated oftener than every eight hours. It should be remembered that the most lasting and dependable way of administering quinin is by mouth.

After the first three or four days of 30 grains of quinin a day for acute attacks, the patient should be given one dose at night before retiring. Since treatment must be kept up for a period of at least eight weeks, it is desirable that it should be convenient and produce the minimum amount of discomfort. There is much more discomfort produced when the patient is up and about than when the patient is at rest. A dose of quinin taken at night does not produce as much discomfort, in active patients, as a dose taken in the morning. It is much more likely to be remembered and taken at night than at other times of the day.

(4) *Frequency of Administration.*—To insure ample concentration of quinin in the blood stream to kill all parasites in the circulation during the acute stage, it should be administered as often as once every eight hours, but after the acute symptoms have passed it is not necessary to administer more than one dose per day for final disinfection. The drug being slowly absorbed and slowly eliminated, especially in patients whose bowel actions are normal, a sufficient concentration is present in the blood at all times to destroy parasites if one dose a day is taken.

(5) *Duration of Treatment.*—Some people are disinfected of malaria parasites by taking quinin for only a few days. A larger per cent. are disinfected by taking it for two weeks. A still larger number, perhaps about 60 per cent., require four weeks' treatment. The best information the author can obtain indicates that more than 90 per cent. are disinfected by taking quinin systematically for a period of eight weeks. It would probably take between three and four months to dis-

infect 100 per cent. With these facts before us, it is very apparent that we must strike some middle ground between a very short period of treatment, in which only a small per cent. are disinfected, and the other extreme, the three or four months' treatment necessary to disinfect 100 per cent. The author's opinion is that for routine purposes all malaria patients should be put upon eight weeks' treatment. None should have a shorter period of treatment. By careful inquiry into the history, we can usually recognize a good many of the resistant, difficult cases to disinfect who would comprise the remaining 10 per cent. not disinfected after eight weeks' treatment. Most of such cases give a history of previous treatment followed by relapse. Any case thought likely to be a resistant one and to require longer treatment should be given treatment at the outset accordingly. Two, four or six weeks should be added to the usual eight weeks' treatment. This must be done without intermission. If, for instance, a patient takes treatment for eight weeks and then after stopping, relapses, the full eight weeks' treatment must be repeated and the additional time added to it. The first course of treatment, which failed, is of no value. This is a fundamental principle affecting the treatment of any disease by means of a specific, which is not generally recognized or appreciated. To give insufficient treatment and wait for a relapse to indicate whether the patient has been disinfected usually results in necessitating a needlessly long treatment, in the first place, and, in the second place, exposes the patient to whatever danger there may be in repeated attacks of the disease. It is the duty of physicians, therefore, to inquire, in every malaria case, whether the patient has recently had other attacks of which this is likely to be a relapse and whether the treatment employed was of sufficient duration to have been likely to disinfect the patient. If so, he may conclude that this is probably a resistant case and should give him treatment accordingly.

(6) *Menstruum.*—The 6, 8 and 10 grain doses of quinin are best given in compressed tablets of 3, 4, or 5 grains each. Tablets are more convenient, less expensive and set free their quinin more quickly and more certainly than capsules do. They do not deteriorate with age as is frequently thought. Recently the author secured some quinin tablets from different manufacturers, some of the tablets being as much as seven years old. When dropped in water they crumbled and set free their quinin in a very few minutes. The ½ to 4 grain doses are best given in aromatic syrup of yerba santa. This menstruum greatly reduces the bitter and unpleasant taste and is perfectly satisfactory. A sufficient amount of ordinary sulphate of quinin should be mixed with the syrup so that one teaspoonful contains the desired dose; or in children under one year of age one-half teaspoonful should contain the desired dose.

Quinin in Solution Condemned.—The author believes that prescribing quinin in acid solution is one of the worst mistakes that can be made in the administration of quinin for malaria. There are extremely few people who will take such a dose for a period of eight weeks. Any doctor who has been in the habit of prescribing quinin in solution or who is disposed to do so in the future should investigate the method by taking it himself. He will have to have a good amount of grit to keep it up for the period necessary to disinfect a patient of malaria. To prescribe such unnecessarily unpleasant doses simply defeats the object in view. Nothing could contribute more to the prejudice and objection to the use of quinin than to try to give it to patients in this way.

(7) *Contra-indications.*—There are no contra-indications for the use of quinin in the proper dose for treating malaria, except perhaps extreme idiosyncrasy to the drug. There are some instances in which people are made quite uncomfortable by quinin. In most instances the discomfort consists of ringing in the ears, more or less dizziness and frequently urticaria. Patients under the influence of large doses of quinin feel it very much worse, especially the dizziness, when exposed to heat, as, for instance, if they are working in the field in the hot sun. Usually these symptoms will pass off in a few days if the patient continues to take the drug. The best remedy for the urticaria in patients who are obliged to take quinin is to continue its use. After a few days the effect wears off. It may be necessary for those who are especially susceptible to the drug to take smaller doses for a few days until they can acquire a certain amount of tolerance.

There are many people who imagine they cannot take quinin. This idea is often encouraged by doctors. Patients who say they cannot take quinin are frequently given quinin disguised in some way and then they do not feel the effect at all. It is much better in the majority of instances to tell the patient frankly that there is no way of masking the unpleasant effect to any extent and that the proper thing is to overcome it by continuing to take the drug. At any rate, he should be informed that it is a choice between malaria and quinin; it is usually not difficult for him to make the decision. Doctors ought to refrain from encouraging patients in their fancy that they cannot take quinin. It is especially bad to give hypodermics of quinin to people who fancy that they cannot take it by mouth. It is not practical to give quinin hypodermically or intramuscularly over a sufficiently long period of time to disinfect patients of malaria. Even if it were practicable, it would still be ridiculous to substitute such a painful and formidable procedure for the simple and eminently successful administration by mouth.

(8) *Antidote.*—In cases of poisoning by quinin taken by mouth, emptying the stomach by means of the stomach-tube, vomiting induced by tickling the fauces, or any other method of eliminating quinin from the stomach should be resorted to. In cases of poisoning by overdoses of quinin given intravenously, stimulants, especially **strychnin**, are indicated.

SURGICAL INDICATIONS.—The only surgical treatment that has been employed in malaria is **splenectomy** for very large spleens. The operation is probably never demanded or justified in simple malaria. Proper quinin treatment always results in a gradual but certain reduction of the spleen which, however, sometimes requires many months to return to normal size. This is readily understood when we recall the large amount of insoluble pigment deposited in the spleen which must be broken up and eliminated by a long, slow process.

Management of Convalescence.—In cases of ordinary chills and fever no special management of convalescence is required. There is difference of opinion as to whether iron and other tonics should be given. A good many follow the practice of giving some form of **iron** and possibly **strychnin** as a tonic during the convalescent period. Others employ **arsenic,** believing that it has some specially beneficial effect in malaria. In fact, there was a time when it was believed that arsenic was actually curative in malaria. There is no good ground for its use, however, in the presence of the much more certain and beneficial drug, quinin. The author's opinion is that plenty of fresh air and nutritious diet is all the tonic that is needed during the convalescence of any ordinary case of malaria. The very severe pernicious cases are sometimes followed by more or less prolonged and tedious convalescence. The anemia that occurs is sometimes very marked, and considerable time is required to rebuild the lost blood. The most important thing of all is to keep the patient constantly under proper quinin treatment. One must be guided by the conditions in the individual case as to the duration of rest following attacks of pernicious malaria. Usually in such cases the patient should be kept in the hospital for at least a week or two following a return to normal temperature. Although rest, fresh air and nutritious diet are by far the most important factors in rebuilding the lost blood, the author believes that arsenic, perhaps in the form of Fowler's solution, 5 to 10 minims t.i.d., may possibly be of additional service following exceptional pernicious attacks.

It is the duty of a physician who has the responsibility of a case of malaria, to advise the protection of the patient against the bites of mosquitoes in order to avoid the danger of transmission during the first few days, which includes the convalescent period. The vast majority of cases are non-infectious after the first day or two of proper quinin treatment, but a few remain malaria carriers and a potential source *of infection for mosquitoes for at least a week or two after the fever is stopped, regardless of the amount of quinin that may be taken.*

Prognosis.—As to Recovery.—The prognosis of malaria is influenced to such an extent by different factors, especially by the clinical type of infection and the treatment the patient is undergoing, that it is difficult to make any definite statement with regard to it. The types of malaria which occur in some localities where the disease is quite prevalent are seldom fatal provided the patient is given quinin, especially if he receives proper doses. In other localities or countries, the disease is much more fatal, due perhaps to the predominance of the estivo-autumnal parasites, which give rise to nearly all cases of pernicious malaria. It can be stated confidently that practically no malaria patients die except those who do not receive proper treatment or those who are too far advanced before treatment is instituted. It is abundant evidence of incompetency for a physician to lose malaria patients who have been under his care for any considerable length of time.

In a general way, it may be said that the more extensive the use of quinin in the treatment of malaria, the lower the mortality, and that the less use made of quinin, the greater the mortality. In some of the tropical countries, in which conditions for the transmission of malaria are most favorable and where there is little use of quinin on account of ignorance or on account of prejudice against its use, as is frequently the case, the mortality is quite high. In other regions, such as, for instance, the southern part of the United States, in which quinin is rather extensively used for the treatment of all acute attacks of malaria, although frequently ineffectively, and where the conditions as to intelligence, etc., are more favorable, the mortality from the disease is extremely low.

The great variation in the mortality from malaria in different parts of the world is illustrated in Table 7 given by Deaderick.[3]

TABLE 7.—DISTRIBUTION OF MALARIA BY COUNTRIES. (*Deaderick.*)

Author	Locality	Cases	Deaths
Laveran	Turko-Russian War	140,000	1,092
Laveran	Constantine	1,310	......
Laveran	Italian Army	4,856	13
Schellong	New Guinea	1,954	22
Ross	Greece	960,048	5,916
Ross	Hong Kong	7,352	984
Ewing	Camp Wikoff	605	39
Smart	Civil War	1,373,355	15,423
Travers	Malay States	3,397	348
Terburgh	Dutch Indies	2,308,128	114,490
Cardamatis	Athens	22,618	15
Koch	Grosseto	281	......
Koch	East Africa	63	2
Hagen	Papua	301	23
British Colonial Reports	British Colonies	12,617	618
Wright	British Malaya	17,468	680
Haw	Baberton	449	14
Hope	North Bengal	1,784	......
Laveran	Algiers	98,774	7,432
Gorgas	Panama	1,055	5
Erni	Dutch Indies	116,879	731
United States Marine Hospital	General	6,618	20
Various Hospital Reports	Southern States	1,294	30
German Protectorate Reports	German Protectorates	5,003	32
Malaria Society	Italy	22,792	120
		5,109,001	148,049

This table indicates an average mortality of 2.89 per cent. for the different parts of the world represented. That it may be far from dependable is indicated by a comparison of definite information as to the mortality in Sunflower County, Mississippi, with the stated mortality of the southern states, of approximately 2.3 per cent.

Sunflower County, Mississippi, shows almost as great a prevalence of malaria as any other county in the southern states. The incidence is about equally divided between the tertian and the estivo-autumnal type. The physicians of the county reported an average of 8,236 cases per year during the five year period 1914 to 1918 inclusive. A careful survey in which the history of attacks of malaria during 1917 was obtained from 8,053 persons and computed for the county indicates that 21,756 cases occurred during one year (1918). Blood examination of those who claimed not to have had attacks of malaria showed that a considerable number of those who gave negative histories showed malaria parasites in their blood. The average number of deaths from malaria in Sunflower County during the four year period 1914 to 1917 inclusive was 77 per year. If we base our calculation upon the number of cases treated by physicians, this indicates a mortality of 0.93 per cent. If we base our calculation upon the number of cases indicated by the history of attacks obtained as in our survey, this indicates a mortality of 0.35 per cent. This is certainly the maximum mortality rate from malaria in Sunflower County, which it is believed is a representative locality of the malaria area of the southern states. That it is still somewhat lower than this seems very certain if we include in our calculation those who had malaria parasites in their blood but were not recognized as having the disease because of lack of recognized symptoms, and base our calculations upon the sum of the total number of persons who had attacks of malaria and of those who had parasites in their blood without having had attacks that were recognized. We may conclude from these facts that the mortality from malaria in Sunflower County, which is probably as high as in almost any other part of the southern states, is less than 0.35 per cent. of those who have the disease or infection. There are not many persons in this particular locality who have been disinfected of malaria by quinin treatment, but almost all who have attacks take quinin in some form or other sufficient to relieve or modify the attack and to prevent death. No doubt if quinin were entirely withdrawn from the locality the mortality from malaria would be increased many fold in a comparatively short time.

Not only is the prognosis influenced very largely by the treatment malaria subjects receive in different localities, but it is also influenced greatly by the type of malaria which prevails. In any locality where tertian malaria, due to the *Plasmodium vivax,* is the chief or only type present, there would be very few deaths from malaria. The same is true to a large extent with the quartan types due to *Plasmodium malariæ.* Few deaths are produced by quartan malaria. On the other hand, estivo-autumnal malaria, due to *Plasmodium falciparum,* is far more destructive than either of the other two. Practically all cases of pernicious malaria are produced by falciparum and almost all the deaths from malaria occur in what are commonly called pernicious cases. The high mortality in pernicious cases is indicated by the instructive table copied from Deaderick[3] (Table 8).

TABLE 8.—MORTALITY IN PERNICIOUS CASES OF MALARIA. (*Deaderick.*)

Author	Number of Cases	Number of Deaths
Laveran	104	53
Bailly	886	341
Nepple	14	6
Antonini and Monard	39	9
Maillot	186	38
Grall	117	75
Burot and Legrand	210	142
Smart	16,209	4,164
Travers	260	81
Martirano	19	9
Pezza	2	1
Tanzarella	31	8
Thayer and Hewetson	3	2
Plehn	10	1
Maillot	7	6
Theophanidis	5	2
Cardamatis	3	2
Pampoukis	52	20
Billet	40	2
Segard	24	15
Maurel	156	77
Caccini	135	56
Matirano	6	3
Charity Hospital, New Orleans	8	6
Neer	3	3
Celli	8,032	1,879
Cardamatis	50	9
Colonial Reports	252	133
Kelsch and Kiener	89	51
Albini	87	11
	27,039	7,205

The very great difference in the mortality as reported by the different observers here quoted is no doubt due largely to the difference in classification of clinical types by the different authors. If it should occur, as no doubt it does, that one observer classes as pernicious cases only those of the most extreme type, the mortality would be much higher in his group of cases than it would be in the pernicious cases of another observer who included in the particular classification a larger number of milder cases. There is no hard and fast dividing line between pernicious and non-pernicious cases.

The mortality from malaria in children is considerably higher than in adults except that it is also high in the case of old persons. There is a great variation in the resistance of different individuals to the effect of malaria. Perhaps one explanation for this is the fact that where malaria prevails to a great extent those who are especially susceptible to its destructive effect die while quite young and do not reach maturity. This is confirmed by the fact that in a locality where malaria is very prevalent the adult residents seem to have milder forms of the disease than children, whereas adults who come from non-malarious regions have much more severe attacks, which often, in the absence of proper treatment, result fatally. It may be, therefore, that there is not actually any difference in the destructiveness of the disease in individuals of different ages, provided they have not previously acquired any degree of immunity or resistance by previous attacks.

Race is also thought to play a part in the mortality from malaria. For instance, in the southern states the mortality rate among the negroes is generally believed to be lower than it is among the whites. A much larger per cent. of the negroes have acquired resistance by previous attacks, than is the case with the whites, because the infection is 33⅓ per cent. greater in negroes. The greater prevalence of the infection among negroes would result in a larger per cent. of immunity or resistance and therefore in a somewhat lower mortality per case or attack.

Certain races are much more prejudiced against the use of quinin than are others. For instance, the Spanish people in Latin America are as a rule very disinclined to use quinin, and it is with difficulty that they can be induced to take it. The author's attention was called to this very forcibly while he was engaged in research work in the Ancon Hospital in Panama. Dr. Henry R. Carter stated that not only was it practically impossible to induce the Spanish laborers to take quinin after they left the hospital, but that they frequently had to be watched to keep them from throwing away what was given them in the hospital. The solution of quinin was used, it seems, for the purpose of making it more difficult for them to throw it away or to deceive the nurse when it was being administered, as well as perhaps because it was thought that it was more effective. The author is inclined to think that the use of quinin in solution perhaps did more harm than good. There are not many people who will continue to take it for any length of time in this form.

As to Function.—Whenever recovery from malaria takes place, it is complete and usually very rapid so far as function is concerned. Long before the patient is disinfected, he appears to be perfectly well. After pernicious cases, it may be considerably longer before the normal is regained, especially in the case of the spleen and liver. The spleen remains enlarged for many months in those cases in which it has been considerably enlarged as it sometimes is. With proper quinin treatment, however, the size of the organ reduces steadily, and in from a few months to a year it returns to the normal size. In cases in which there has been a great deal of deposition of pigment in the tissues, it is sometimes a month or two before this has been entirely removed and the complexion has returned to the normal. Large quantities of pigment are present in the spleen for many months after all parasites have been destroyed. However, this does not seem to affect the function of the organ seriously, if at all. The same thing can be said of the liver, except that it contains less pigment and probably clears more rapidly.

Pathology.—The most important changes in malaria are those affecting the blood and especially the red blood-cells. Malaria does not affect the leukocytes to any considerable extent. The only notable change in the leukocytes is an increase in the percentage of large mononuclear cells. This is due to an effort of nature to supply an increased number of cells in order to phagocyte the pigment and perhaps the parasites set free by the segmentation of the schizonts. The increase may run up to 20 or 30 per cent., although in most cases of malaria the large mononuclear cells do not exceed from 10 to 15 per cent. The normal is from 1 to 8 per cent.

In pernicious malaria there is frequently a leukocytosis running as high as 15,000 or 20,000 in some cases. Whenever leukocytosis occurs, it is also accompanied by an increase in the neutrophil count.

Since every parasite, as it matures, destroys at least one red blood-cell and since countless millions of parasites mature at the time of occurrence of every malaria paroxysm, this destruction of red blood-cells soon leads to more or less anemia. Some think that the anemia is out of proportion to the number of parasites present. Lawson[29] has offered observations in support of her belief that the anemia which appears to be out of proportion to the number of parasites is due to the fact that individual parasites migrate from one cell to another and that a single parasite damages many cells. The anemia is frequently out of proportion to the number of parasites in the peripheral circulation, but the number found in blood smears does not necessarily indicate the number present in the individual.

Most of the malaria parasites in an infected person are lodged especially in the capillaries of certain organs and tissues, but to a certain extent in the capillaries of the entire body. Those which are present in the peripheral circulation are either very young and small parasites or parasites that have temporarily escaped from lodgment in the capillaries. One cannot estimate the number of parasites present nor the amount of blood that will be destroyed by a given number of parasites in the circulation.

The anemia is due to a reduction in the total number of cells and a further reduction in the hemoglobin content of the individual cells. The color index is always below normal in uncomplicated malaria.

FINDINGS AT AUTOPSY.—The *skin* of subjects who have died of acute malaria usually presents a dusky, brownish hue which is more pronounced the longer the disease has lasted.

The *spleen* shows the most marked changes, perhaps, of any organ. It is always more or less enlarged. Enlargement is greater in tertian than in estivo-autumnal malaria and it is greater the longer the duration of the disease. The color is grayish and reddish brown. The capsule strips easily in most instances. The organ is usually soft and pulpy. There is enlargement of the malpighian corpuscles, sometimes giving the appearance of sago spleen. The cut surface shows the very much darkened tissue due to the presence of enormous quantities of pigment. Microscopic sections show the large mononuclear cells and giant cells to be heavily pigmented. The malpighian bodies show the greatest quantities and largest masses. The walls of the small vessels are thickened and the lumen is frequently obliterated by enormous numbers of parasites contained free within the lumen as well as within the cells lining the vessel. Smears of pulp from the spleen show large numbers of parasites, red-cell débris and pigment. One receives the impression from studying such preparations and also from studying suitable sections from the spleen that not only are there many dead parasites in the spleen but also that there is growth and development there. In cases dying of some other disease, but which have latent or old malaria infection, the spleen usually shows more or less enlargement and pigmentation, depending upon the duration and extent of the latent malaria. Sections show pigment in the cells and also parasites in the small vessels and possibly in the cells. Frequently parasites can be found by examining smears from such spleens where none could be found in blood-smears during life.

The *liver* is enlarged and congested in all cases in which death is due to malaria. It is usually of a dark or brownish color due to the pigment it contains. Microscopic sections show collections of pigment in the capillaries, which are frequently well marked by its presence in the endothelial cells and also between the vessel-wall and the adjoining liver-cells. The small blood-vessels are frequently plugged or entirely clogged by the collection of parasites and pigment in their lumen. In the case of patients dying of other disease where latent malaria is present, more or less pigment and parasites can usually be found in the liver, not to the same extent, however, as they are found in the spleen. Cirrhosis is seldom if ever produced by malaria.

The *kidneys* are usually more or less congested, and are softer than normal in the case of patients dying of malaria. The capsule strips easily and the medullary pyramids sometimes show minute hemorrhages. There is usually cloudy swelling and other damage to the endothelial cells lining the convoluted tubules. The cells lining Bowman's capsule are usually not affected. The tubules are frequently more or less plugged with casts. Certain of the capillaries are plugged with parasites and pigment, but to nothing like the same extent as is found to be the case in the spleen, liver and even in the brain.

In the case of patients dying of hemoglobinuria, the kidneys usually show special pathology in addition to that found in ordinary acute malaria. The lumen of the loops of Henle is usually choked with casts of hemoglobin and with endothelial detritus. Since most cases of hemoglobinuria in which death occurs show suppression of urine, the tubules are plugged with casts in almost all cases. Aside from the more intense processes in the kidney and the greater jaundiced or yellowish appearance of all tissues, there is little difference between the autopsy findings in hemoglobinuric fever and those in other pernicious forms of malaria. It frequently occurs, however, that the evidence of parasites is less, but they are always found in malarial hemoglobinuria.

Localization of malaria parasites in the *brain* is one of the chief causes of death from malaria. Frequently at autopsy sufficient pigment is found in the brain to give a grayish or slaty appearance. There is perhaps no organ in which localization of malaria parasites in the capillaries can be as satisfactorily demonstrated as in the brain. The cut surface sometimes appears grayish as a result of the large amount of parasites and pigment present in the capillaries. Smears or contact preparations show capillaries plugged for long distances with parasites, most of which are attached to or within red blood-cells. Some, however, appear to be entirely free from blood-cells. Parasites are found in all stages of development, and in autopsies made soon after death the parasites in such specimens still stain well. No doubt they live for many hours in the cadaver. Cases in which coma or other cerebral symptoms are prominent features show the largest proportion of capillaries obstructed by parasites. As a matter of fact, the coma is produced, in the author's judgment, by the anemia of the brain resulting from the obstruction of large numbers of capillaries. Occasionally hemorrhages and thrombi are found, but these are rather rare. Hemorrhages are probably due to the rupture of obstructed capillaries.

The entire *vascular system* is greatly affected by malaria because of the fact that the development and reproduction of the parasites takes place within it. The endothelial cells lining the entire vascular system destroy the parasites and pigment, but it seems that the smaller the vessels, the more of this takes place. However, in vessels too large to be obstructed, we find that large numbers of endothelial cells lining the walls contain pigment. In most instances where death is due to malaria the capillaries of some vital organ or organs are plugged with parasites and débris from their reproduction. It is this plugging of the capillaries of one organ or another that produces many of the symptoms in pernicious malaria. For some reason or other, the parasites collect in the capillaries of certain organs of an individual much more than they do in others. For instance, in some cases the parasites collect in the brain especially, giving rise to comatose or other cerebral forms of malaria. In other instances the parasites collect especially in the capillaries of the stomach or intestines, giving rise to a form accompanied by prominent gastro-intestinal symptoms, such as nausea, vomiting and diarrhea.

Even the capillaries of the skin contain large numbers of parasites and large quantities of malaria pigment, especially in chronic cachectic cases. This is sufficient in many instances to give rise to the peculiar yellowish or brownish appearance of the skin of severe chronic malaria cases. In rare instances even the cardiac capillaries are plugged with parasites.

In autopsies in hemoglobinuric cases the heart-muscle is frequently soft and flabby and upon microscopic examination is found to have undergone more or less fatty degeneration.

The changes in the *bone-marrow* are among the most striking found at autopsy in acute malaria. The marrow is frequently of a brownish, chocolate color due to the presence of large amounts of pigment. This discoloration depends largely upon the severity and duration of the infection. The pigment consists not only of that present in parasites but also of that retained from the segmentation of other parasites. Microscopic sections show many of the vessels to be plugged with parasites and pigment. Here are found the largest number of developing gametes. In cases of estivo-autumnal infection, gametes show all stages of development, if they are present at all. The macrophages frequently contain large quantities of pigment granules, in many instances as much pigment as would be produced by twenty-five or fifty parasites.

The *lungs* show the presence of a larger or smaller number of parasites and of pigment in the capillaries, in autopsies on cases dying of severe acute malaria. There seems to be considerable variation in the collection of parasites and pigment in the lungs, but these organs do not offer as favorable conditions for the collection of pigment as do other organs and tissues.

Autopsies on cases of pregnancy dying of acute malaria, or on cases of abortion from malaria, usually show very large numbers of malaria parasites in the maternal vessels of the placenta. In fact, a study of the sections indicates that the life of the fetus is destroyed by interference with its nutrition through the plugging of the capillaries by parasites and débris from their reproduction.

The *suprarenal glands* usually contain many plasmodia, pigmented leukocytes, and a few macrophages. Some of the vessels are distended or dilated, apparently as a result of obstruction further on. Craig says that "a few of the adrenal cells may contain pigment and infected corpuscles."

Historical Summary.—One has only to look at the malaria maps of the world showing how the malaria zone belts the earth to know that its existence goes much further back than we can trace it historically. The ancient Egyptians were familiar with malaria, according to Groff, and the word *"aat,"* which is found among the inscriptions of the temple of Denderah, is believed to refer to malaria. Deaderick says that more than one thousand years before the birth of Christ malaria is mentioned in the Orphic poems. Hippocrates gave a good description and classification of tertian, quotidian and quartan malaria. Plautus, who died in 184 B.C., wrote about what is believed to have been malaria in Italy.

The first important epoch in the history of our knowledge of malaria dates from the discovery of Cinchona bark and its action in malarial fever. Peruvian bark was introduced in the middle of the seventeenth century. Torti and Morton divided the fevers into two classes,—those which were cured by the bark, and those which were not. They had in their hands at that time the therapeutic diagnostic test which is used to a very great extent at the present time.

Pelletier and Caventou, in 1820, succeeded in isolating quinin, the most important alkaloid of Cinchona bark.

The discovery of the malaria parasite was made by Charles Louis Alphonse Laveran on November 6, 1880, and announced to the Paris Academy of Medicine, November 28, 1880. It was many years before his work was accepted and among the last countries to accept it was his own—another instance in which "a prophet is not without honor save in his own country." The idea that malaria is disseminated by insects, including mosquitoes, had been suggested from time to time by Koch, in 1884, Laveran, in 1884, Flügge, in 1891, Manson, in 1894, and by Bignami, in 1896. No doubt many others advanced the same idea from time to time, but the fact was finally proven by Ross, in 1898, following the suggestion of Manson. Ross's discovery marks the beginning of a new epoch in the history of our knowledge of malaria, and stands out as one of the most important, if not the most important, discoveries ever made in connection with this perhaps most important disease of the world. Upon his discovery most of the malaria control that has ever been accomplished is based. It has already contributed to the progress of civilization more than can be told.

Deaderick and Thompson did me the honor of saying that "Bass's discovery of the method of cultivating the malaria parasites (in 1912) is the most important land-mark in the history of malaria since the discovery of Ross." Whether this proves to be true depends largely upon the use to which the cultivation of malaria parasites in vitro may be put in the future. Fortunately the author's work has been confirmed in nearly all civilized countries of the world.

Geographical Distribution.—No description of the geographic distribution of malaria throughout the world that can be made would present the facts in as readable and useful form as would the three maps taken from Mannaberg's studies on malarial disease in Nothnagel's Encyclopedia of Practical Medicine. It will be seen that the malaria zone belts the globe and that the disease is more frequent as the equator is approached from each direction (Figs. 17, 18 and 19).

Sociological Aspect of Malaria.—Up to the present time the sociological aspect of malaria has not been properly emphasized. Although it has been appreciated that it is largely a community disease, the extent to which it is a family disease has not received sufficient attention.

MALARIA AS A COMMUNITY DISEASE.—Although mosquitoes capable of transmitting malaria are widespread, their flight and life habits are such as to prevent their transmitting malaria at long distances from their source of infection. A given individual who is a malaria carrier in a community is not likely to be a source of infection beyond from half a mile to a mile from his own residence. In a community where a large proportion of the population are infected with malaria, there are many sources of infection of mosquitoes and therefore there is great probability of its transmission. One who lives in a malaria community runs greater or less risk of becoming infected, according to the number of malaria carriers living in the community. Every malaria carrier in the community is a menace to the health of the community and should be looked upon as such, just as a case of leprosy, small-pox, diphtheria, etc., would be. Since the infection is curable by means which are not beyond the reach of all, there is little excuse for anybody's remaining a malaria carrier. He is an unnecessary source of infection.

The control of malaria on a large scale will ultimately be made a community problem. In communities where it is possible to prevent or control mosquitoes, this can be made a community undertaking. In

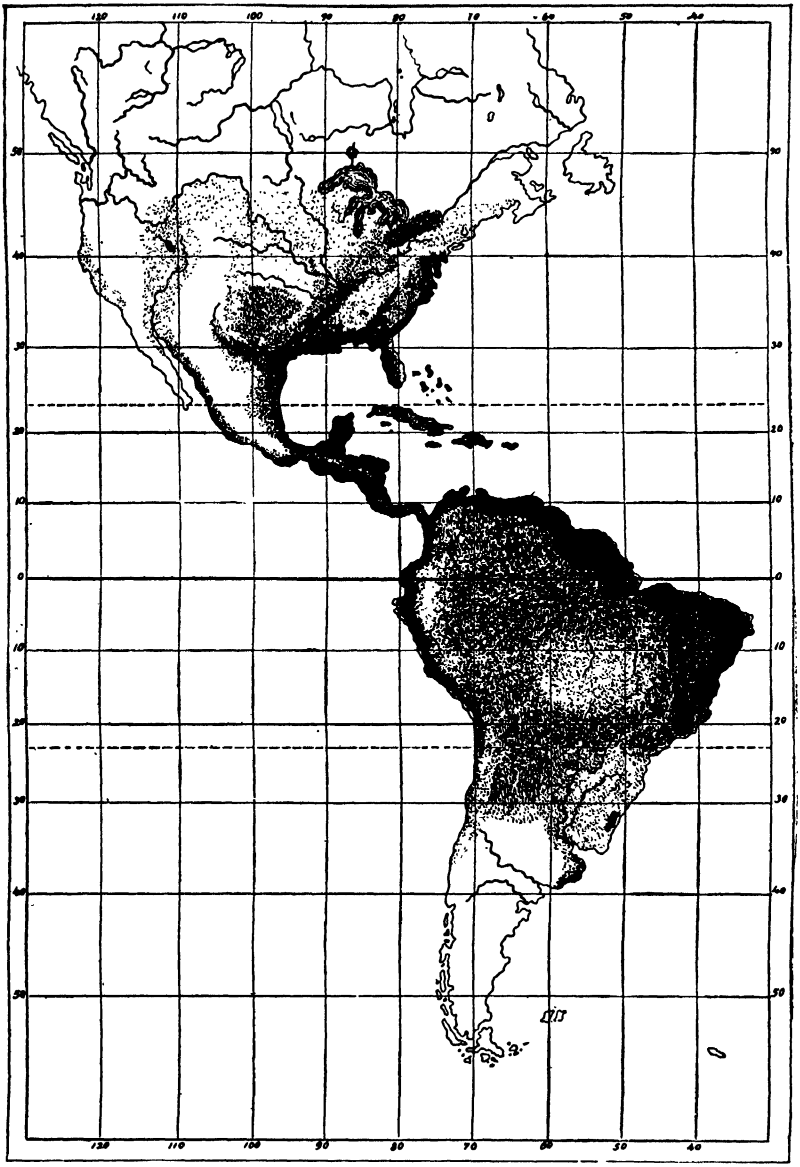


FIG. 17.—SHOWING THE DISTRIBUTION OF MALARIA AS INDICATED BY THE INTENSITY OF THE SHADING. (Mannaberg, in Nothnagel's Encyclopedia of Practical Medicine, W. B. Saunders & Co.)

communities where the difficulties in the way of mosquito control are sufficiently great to make it impractical or difficult to carry out, it is still possible to control malaria by disinfecting the infected persons with proper quinin treatment.

In the demonstration of malaria control by disinfecting infected persons in Sunflower County, a community of 100 square miles, containing approximately 9,000 people, has practically eradicated malaria in one year's time. This demonstrates some of the possibilities along this line, and indicates what a great reduction in the prevalence of malaria will result in any community where sentiment can be created against persons remaining malaria carriers. Sooner or later those who are interested must know that every malaria carrier in a community is a menace to the health and life of those who live in the community.

Although malaria-infected persons are likely to be a source of infection to all the residents in a community, they are especially dangerous to their own families. A person who has malaria is likely to infect mosquitoes, which, after depositing their eggs and developing their parasites to the infectious stage, are most likely to return to the same house to feed again. In this way they are much more likely to infect other members of the same family than to infect other persons in the same community. If people with a proper sense of responsibility who are infected with malaria realized the danger of transmitting their infection to other members of their own families, causing sickness and perhaps death, they would be much more interested in thoroughly disinfecting themselves than they are at present.

The author believes that this is one of the responsibilities that a doctor who treats a case of malaria should recognize and assume. Not only should the patient be advised and given treatment to disinfect him for his own health, but he should be informed of the great menace he is to the health and life of his family as long as he remains infected. There are not many mothers and fathers who would continue to carry infection or permit other members of their families to do so if they realized what it means to the life and health of the other members of their families. If the author, knowing what he does about malaria, should live in a malarious community and neglect to disinfect himself or any member of his family who might be infected, he would feel a great sense of remorse if another should become infected and perhaps die as a result. If public health workers who are endeavoring to control malaria would make more use of this idea of the greater probability of transmission in the family of the patient himself than elsewhere, it would be found to be a strong argument in support of the thorough disinfection of individuals.

REFERENCES

Below are listed a few references of which special mention has been made in the text. Many others that have been referred to have not been listed here. It is considered that it would be out of place to give a complete bibliography of malaria. A partial one would be of only limited service. For complete bibliographies the reader is referred to Mannaberg in Nothnagel's Encyclopedia of Practical Medicine, American Edition, 1905, W. B. Saunders and Company, Philadelphia; Deaderick's Practical Study of Medicine, 1905, W. B. Saunders and Company, Philadelphia. During the past few years the Journal of the American Medical Association has listed practically all the articles on malaria of value in the English language and many of the foreign articles. One who has occasion to look up references to the literature on malaria should consult these references.

1. Hoffman, Frederick L., LL.D., Statistician The Prudential Insurance Company of America. A plea and a plan for the eradication of malaria throughout the western hemisphere. Prudential Press, Newark, New Jersey, 1917, p. 6.
2. Public Health Reports, Reprints. Louisiana, No. 414; Kentucky, No. 415; Eastern Texas, No. 419; Florida, No. 446; South Carolina, No. 449; Arkansas, No. 451.
3. Deaderick, Wm. H. A practical study of malaria. W. B. Saunders & Co., Philadelphia, 1909.
4. Mannaberg, Julius. Nothnagel's Encyclopedia of practical medicine, Am. Ed., W. B. Saunders & Co., Philadelphia, 1905.
5. James, W. M. Notes on the etiology of relapse in malarial infections. Jour. of Infect. Dis., 1913, xii, No. 3, 277.
6. Osler. Anniversary volume, 1919, published by Paul B. Hoeber, New York.
7. Bass, C. C. A new conception of immunity: its application to the cultivation of protozoa and bacteria from the blood and to therapeutic measures. Jour. Am. Med. Assn., 1911, lvii, 1534.
8. Bass, C. C., and Johns, Foster M. The cultivation of malaria plasmodia (*Plasmodia vivax* and *Plasmodia falciparum*) in vitro. Jour. Exper. Med., 1912, xvi, No. 4, 567.
9. Bass, C. C. Cultivation of malaria plasmodia in vitro. Am. Jour. Trop. Dis. and Prev. Med., 1914, i, No. 8, 546.
10. Deaderick, Wm. H., and Thompson, Loyd. Endemic diseases of the southern states. W. B. Saunders & Company, Philadelphia, 1916.
11. Griffitts, T. H. D. Winter hibernation of *anopheles* larvæ. U. S. Pub. Health Rep., 1918, xxxiii, No. 46, 1996.
12. King, W. V. *Anopheles punctipennis* a host of tertian malaria. Am. Jour. Trop. Dis. and Prev. Med., 1916, iii, No. 8, 426.
13. LePrince, J. A., and Orenstein, A. J. Mosquito control in Panama. G. P. Putman's Sons, New York and London, 1916.
14. LePrince, J. A., and Griffitts, J. H. Studies of the distance of flight of *Anopheles quadrimaculatus.* U. S. Pub. Health Repts., 1917, xxxii, No. 18, 656.
15. Mitzmain, M. B. Is mosquito or man the winter carrier of malaria organisms? U. S. Pub. Health Bull., 1916, No. 84, 27.
16. Barber, Marshall A. The Philippine Jour. Sci., No. 1, Sec. B, Trop. Med., Jan., 1918, xiii.
17. Mitzmain, M. B. U. S. Pub. Health Repts., Sept. 1, 1916, xxxi, No. 35.
18. Marchiafava and Bignami. Quoted in Castellani and Chalmers, Manual of Tropical Medicine, 2nd Ed., 1910.
19. Craig, C. F. The malarial fevers. Wm. Wood and Company, New York, 1909.
20. Davis, Wm. T. Ocular complications of malaria and the toxic effect of quinin upon the eye. Southern Med. Jour., 1916, ix, No. 9, 769.
21. Stephens, J. W. W. The anti-malaria operations at Ismailia. Ann. Trop. Med. and Parasitol., 1911, v, No. 2, 215.
22. Derivaux, R. C. Malaria control: a report of demonstration studies conducted in urban and rural sections. Pub. Health Bull., 1917, No. 88, 49.

23. Stephens, J. W. W., Yorke, W., Blacklock, B., Macfie, J. W. S., Cooper, C. Foster, and Carter, H. L. Studies in the treatment of malaria. IX. A comparison of the results of interrupted and continuous quinin treatment. Ann. Trop. Med. and Parasitol., 1918, xi, No. 4, 359.
24. Taylor, H. A. Malaria control demonstration at Hamburg, Arkansas. Southern Med. Jour., 1919, xii, No. 2, 74.
25. LePrince, J. A. Mosquito control about cantonments and ship yards. Pub. Health Repts., 1919, xxxiv, No. 12, 547.
26. Darling, Samuel T. Studies in relation to malaria, 1910, p. 32. Gov. Printing Office, Washington, D. C.
27. Celli, Prof. Angelo. The restriction of malaria in Italy. Tr. 15th Internat. Congr. Hyg. and Demography, 1912, v, pt. 2, 516.
28. Bates, John Pelham. A review of a clinical study of malarial fever in Panama. Jour. Trop. Med. and Hyg., 1913, xvi, No. 14, p. 209.
29. Lawson, Mary R. Migration of parasites as the cause of anemia in estivo-autumnal infections. Jour. Exper. Med., 1919, xxix, No. 4, 361.

PRACTICE OF MEDICINE—TICE

Insert in your Volume III these pages 649—662 immediately following Page 648.

CHAPTER XX

SAND-FLY FEVER

By Edgar Erskine Hume, M.A., M.D., LL.D., Dr.P.H., D.T.M.

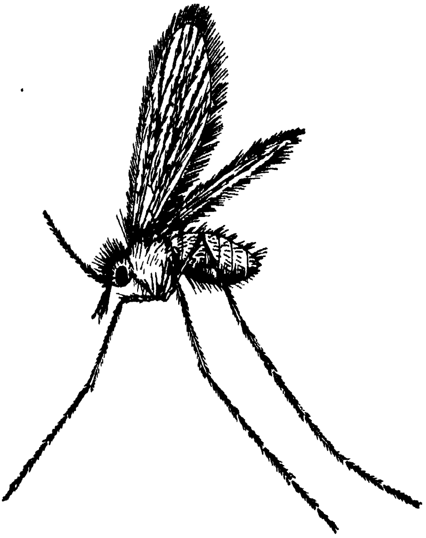
Synonyms.—Pappataci fever, Phlebotomus fever, three-day fever, summer influenza, summer fever, Mediterranean dengue, Macedonian fever, Skoplje fever. It is of interest to note that the Arabic name for the disease "Yokos wa yuskut" picturesquely means "to bite and say nothing," referring to the almost painless bite of the sand-fly. The Italian term "Pappataci" has somewhat the same significance.

Definition.—An acute tropical and subtropical fever characterized by an acute onset, a sudden rise of fever with duration of three days, fall by lysis, practically no mortality, and transmitted by the bites of several species of Phlebotomus.

Etiology.—Virus.—The disease is produced by a filterable virus which has not yet been isolated. The causative agent is present in the blood during the early stages of the disease, the patients being infective during the first day but not later. This was demonstrated conclusively by Doerr and Birt. Sand-flies which had been permitted to bite persons suffering from the disease were transported to Vienna and Netley respectively, where the genus is unknown. The insects were then made to bite fresh subjects with the result that a number of such individuals developed the disease. These experimental infections were produced provided that the sand-fly had first bitten the fever-stricken patient within 24 hours after the onset of the disease, and then only if seven days had elapsed between the two stages of the experiment. Thus, it seems that the virus undergoes some cycle in the body of the vector. Blood taken from sand-fly fever patients may be kept *in vitro* for several days and still retain its infective property, even after having been passed through a Chamberland filter.

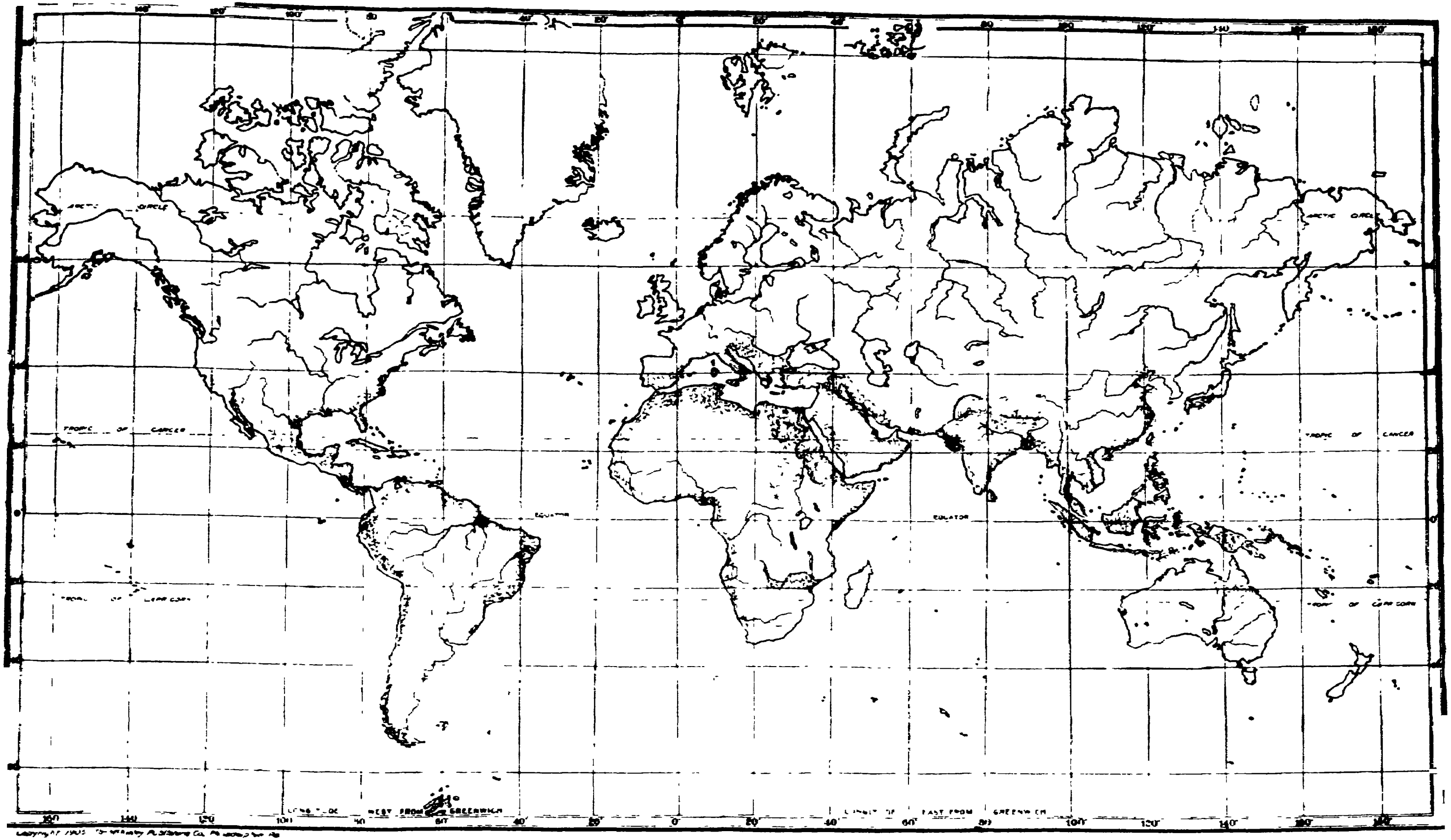
Transmission.—The disease is transmitted by the bite of various species of the sand-fly or Phlebotomus, the most common being *Phlebotomus pappatasii* and *Phlebotomus minutus*, though many other species have been described. The female only is the blood sucker. The virus is transmitted from parent insects to their offspring or by the young eating the excreta or the dead bodies of their parents and others. It has been abundantly proven since the experiments of Doerr and Birt that if sand-flies are absent from a locality, the disease is also absent. Patients often claim that there are no sand-flies where they live but a careful search during the day nearly always reveals them. In houses they are to be found in dark places near the cornice or behind hangings. The insects are of such small size that they readily pass through the ordinary mosquito netting and so escape in the morning. The bite is not painful and frequently does not awaken the sleeper.

Life History of the Phlebotomus.—The female deposits her eggs, 40 to 50 in number, in dark, rather damp places where organic matter is available as food for the larvæ. The eggs are laid separately and not in masses, and Newstead's observations tend to show that complete oviposition may require several days for completion and that the females may die before producing their full complement. The eggs are 0.1 to 0.15 millimeter long, elongate oval in form and thinly covered with a viscous substance. They become yellowish-brown in a few hours after deposition, the surface being coarsely reticulated. The adults bite both warm- and cold-blooded animals. Engorgement is rapid and great and in from 36 to 40 hours digestion is complete. The blood is probably an important factor in the production of fertile eggs and a meal is apparently necessary for fertilization. The food of the male Phlebotomus is somewhat uncertain. The length of life of the adult is unknown, though Wenyon succeeded in keeping one female alive for 48 days. They may be transmitted for considerable distances in ships and are undoubtedly distributed by coasting vessels which may account in part for the geographical distribution. Temperature and atmospheric humidity are the chief factors regulating breeding and development. Marrett states that the requisite temperature for active breeding is from 70° to 86° F. (21.1° to 30° C.) and that below 60° F. (15.6° C.) the larvæ become dormant. The conditions necessary for favorable development and the determining factors in the selection of breeding places are (1) the presence of moisture in moderate degree, (2) the absence of light and (3) the presence of nitrogenous organic matter.



PHLEBOTOMUS PAPATASSI. Adults measure from 3 to 5 mm. in length. The position of the wings is characteristic.

OCCURRENCE.—Sand-fly fever occurs during the hot months of the year, a mean temperature of 70° F. (21.1° C.) being necessary for its



THE DISTRIBUTION OF SAND-FLY FEVER

development. Below this temperature the sand-fly cannot go through its proper cycle. From the accompanying map of the geographical distribution of the disease, it will be seen that it is found in all parts of the world, depending only on the prevalence of the necessary temperature. The altitude is important as in localities high above the sea level where the temperature is low the disease does not occur. Lower down on the same mountains or plateaux the disease may be found.

It has been noted that the disease is apt to attach itself to certain buildings and from the fact that persons sleeping in the lower stories are more likely to become infected, it would seem that the insects do not fly high as a rule. A more probable explanation may be that if unprotected individuals are to be found on the lower floors there is no necessity for the sand-flies to go higher in search of blood. The flies live and breed in old walls, cracks and fissures of buildings, in caves, in sand cracks on the ground, etc., a certain amount of moisture as well as darkness being necessary for their development. The larvæ feed on the excretion of bats, lizards and the like, and the adult fly has been seen to feed on these animals. It is usually stated that the sand-fly does not travel far from its breeding place and observation by medical officers of the allied troops in Macedonia, during the Great War, seem to bear out this statement. Some sanitarians go so far as to claim that a building situated more than fifty yards from the breeding places of the fly is relatively immune. The insects cannot withstand any considerable current of air and hence bite chiefly on still nights.

While sand-fly fever is usually an endemic disease, it may at times attain epidemic prevalence. Epidemics vary in severity, not only from time to time but from place to place.

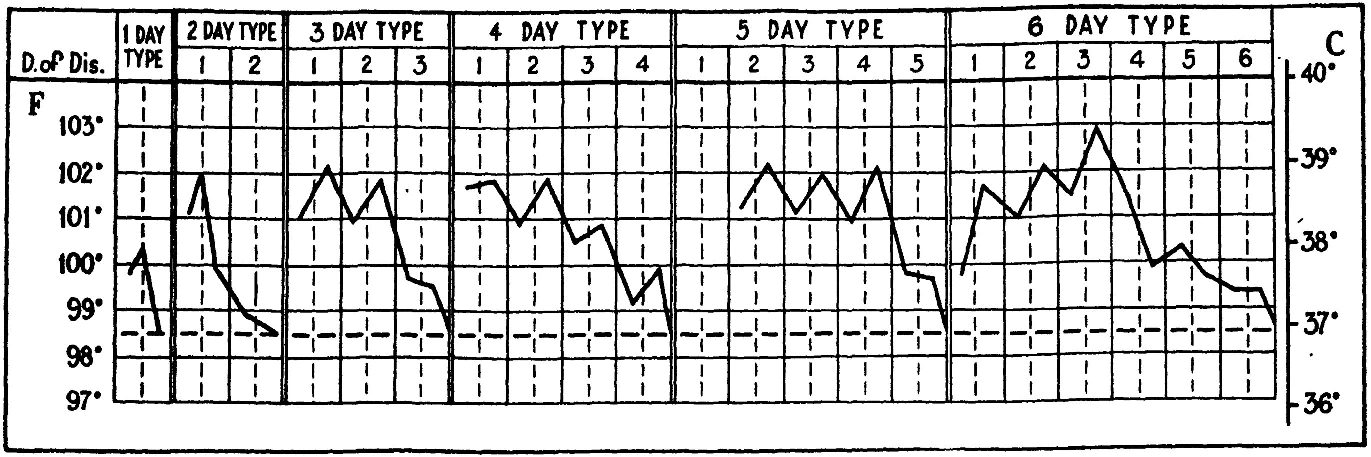
Symptomatology.—INCUBATION PERIOD.—The usual incubation period is from three to seven days. Experimentally the disease has followed inoculation in as short a time as 16 hours, while the longest period is about nine days.

Prodromal symptoms are usually so slight as to cause the patient little or no inconvenience, though in some cases there are muscle-pains, loss of appetite and lassitude.

Onset is sudden, beginning with a slight feeling of chilliness or more rarely rigor and intense frontal headache. The temperature rises rapidly to 103° or 104° F. (39.4° or 40° C.). The character of the headache is important. It is frontal and usually postorbital, the patient complaining that his eyes feel as though they would start from his head. The eyes are quite tender to pressure and there is marked injection of the conjunctivæ. Photophobia usually exists. At times, the injection of the eye may be so marked as to remind one of an infection by the Hemophilus (Bacillus) of Koch-Weeks. The lids are partly closed and if drawn apart the injection will usually be found to extend in a horizontal band across the eyeball rather than covering the whole.

The face and neck are flushed, the redness often being almost a rash. Castellani has described a peculiar feature of this erythema, viz., it persists for 10 to 15 days after the fever has subsided and fades away very slowly. Thus, it is often easy to recognize persons, especially blondes, who have recently recovered from the disease.

The patient may complain of general muscle pains of excruciating character, particularly in the calves and loins. All motion is painful



TEMPERATURE CHARTS ILLUSTRATING TYPES OF SAND-FLY FEVER.

Modified from Birt (J. of R. A. M. C. for March 1910). The graphs are constructed from the mean of many charts.

so that the sufferer is perfectly willing to lie quietly in bed. He is apt to be irritable and to complain at any sounds. Though insomnia may occur, the individual is more likely to be drowsy and even unable to walk on account of the vertigo.

The gastro-intestinal system is disordered. There are severe attacks of vomiting, especially at the beginning of the disease, and persistent constipation. While the vomiting lasts there is marked loss of appetite, the patient in some cases declining food altogether. More rarely there may be attacks of diarrhea with hemorrhage from the bowel. The tongue is heavily coated on the dorsum with white or brown material, but the edges are clean. The liver and spleen are not enlarged, an important diagnostic point.

The throat and palate are usually congested, injected and irritable. The gums and buccal mucosa bleed easily. There may be small hyperemic red spots on the palatal mucosa, but these do not extend to the hard palate.

The blood picture is an early leukopenia which persists well into convalescence, averaging 3,000 leucocytes per c.mm. There is a relative diminution of polymorphonuclear leukocytes and an increase in the large mononuclears. The following may be regarded as a typical blood count:

Polymorphonuclears	61.1 per cent.
Lymphocytes	21.4 per cent.
Large mononuclears	14.2 per cent.
Eosinophils	2.8 per cent.
Transitionals	1.5 per cent.

The urine is of a febrile character but usually clear, acid in reaction and not very highly colored. There is usually no albumin, or if any, only a trace.

On the third day, the temperature falls to normal or subnormal, but there is sometimes a terminal rise. Accompanying the reduction in temperature there is often epistaxis and profuse sweating, a sharp contrast to the dry skin noted in the course of the disease. The heart rate is slowed during the illness. With the return to normal temperature the symptoms usually abate but convalescence is sometimes greatly prolonged. For one to three weeks the patient is debilitated and unable to perform his duties. In this characteristic of the disease lies its economic seriousness to the community.

Diagnosis.—The important points to be borne in mind are the season of the year, the presence of phlebotomi in the locality, the sudden onset, the flushed face and neck, the band-like injection of the conjunctivæ, the pains in the eyes and muscles, the leukopenia, the absence of rash and the rapid rise of fever ending on the third day. An examination of the skin, particularly the wrists and ankles, will usually reveal the sand-fly bites as red punctures often appearing papular.

The disease most likely to be confused with sand-fly fever is dengue and most of those who have had that experience with the two maladies assert that it is impossible to differentiate sand-fly fever from the mild cases of dengue. Dengue is more epidemic in character, the pains are more in the bones and joints, there is a characteristic rash and the fever instead of ending on the third day usually recurs after an afebrile period of a few days. In both diseases there are hemorrhages from the mucosæ and leukopenia.

PRACTICE OF MEDICINE—TICE

Insert in your Volume III these pages 649—662 immediately following Page 648.

Influenza, which resembles sand-fly fever in many ways, is a winter disease; the blood picture is different and the catarrhal symptoms are more pronounced.

Malaria may be diagnosed by the presence of the parasites in the blood, the temperature chart and the enlargement of the spleen. Phillips stresses the complaint of the malaria patient that he has "fever" while the sand-fly fever patient complains of "pains."

Mild attacks of yellow fever with their pains, leukopenia with relative increase of mononuclears and tendency to hemorrhage, may be difficult to differentiate, especially where both diseases are endemic. More severe cases of yellow fever, of course, offer no difficulty.

The diseases of the typhoid-paratyphoid group begin more gradually and are of longer course and we have the assistance of the laboratory in making the blood culture or later the Widal test.

In localities where typhus fever and sand-fly fever are coexistent the diagnosis may offer great difficulty, but the leukocytosis of the onset of typhus affords valuable assistance. The differences in seasonal occurrence are of course significant.

Treatment.—PROPHYLAXIS.—The only way to escape the disease in endemic districts is to avoid the bite of the insect. Attempts should be made to protect both the well individual and the patient from the sand-flies. The Phlebotomus being smaller than the mosquito, the ordinary mosquito net or screen is of no value. Sand-fly nets are manufactured and have meshes so small (40 to 45 to the inch) that the sand-flies cannot pass through. These, however, keep out so much air that their use is attended by great discomfort, so that in the tropics or during very hot weather in the more temperate zones, they are of but little practical value. Camphor and kerosene seem, when placed inside the mosquito netting, to have some value in driving away the insects. Attempts have been made to spray the outside of the mosquito nets with a solution of naphthalene or formalin which have a distinct value in keeping away the insects, but are very unpleasant for the sleeper. Punkahs and electric fans are useful in keeping away the flies, and the removal of bedrooms to the upper stories of buildings is not without its use.

In addition to screening with its disadvantages, the following measures are among those recommended by the Royal Air Force Sand-fly Fever Commission:

(*a*) Free ventilation and artificial air currents. When electric fans or punkahs are employed, they should be directed against the open window.

(*b*) The admittance to the rooms of as much light as possible during the day, the use of powerful electric lamps if practicable until dusk, succeeded by the employment of fans at the windows.

(*c*) Reduction of hiding places. The walls to be rendered as free as possible from hangings, pictures and other articles, the beds to be kept in the best lighted parts of the room, away from the walls. At times the felling of trees in immediate proximity to the house is desirable.

(*d*) Repellents. Besides camphor and kerosene, which have been mentioned, many formulæ have been suggested. These contain chiefly combinations of the oils of anise, eucalyptus and cassia together with materials to form an ointment. Tobacco smoke is an excellent repellent.

PRACTICE OF MEDICINE—TICE
Insert in your Volume III these pages 649—662 immediately following Page 648.

(*e*) Fumigation of the rooms with suitable insecticides, one of the best of which is pyrethrum.

(*f*) Traps. Box traps lined with dark cloths placed high up in the dark portions of the rooms. These should be examined daily and the flies killed with ammonia fumes.

(*g*) Destruction of the breeding of the sand-fly. This is at once the most important and the most difficult measure. Superfluous stone walls in bad repair in the neighborhoods of towns and villages should be removed. Constant supervision of the walls in the proximity of infested areas is required. All holes and crevices, even the most minute, should be filled with cement or other suitable material. Crevices in and near buildings should be watered daily. No heaps of stones, bricks, refuse material, etc., should be tolerated within a radius of 100 yards from the nearest habitation. Rough ground to be cleared of weeds and all holes disclosed to be filled with beaten earth. Gardening should be encouraged.

Certain natural enemies of the sand-fly are known. In Malta, a chelifer attacks the larvæ and the mite and a fungus attacks the adult. McKie has described in India a flagellate protozoon in the intestine of the fly.

MEDICINAL.—The treatment is purely symptomatic. No drugs of value are known other than the various antipyretics, the most satisfactory of which is **pyramidon.** **Aspirin** relieves the pain in some individuals but in others has but little effect. The disease is self-limited and during its continuance the patient should be kept at complete rest in bed and on soft diet.

Complications and Sequelæ.—These are not as a rule serious. The most important is the weakness which characterizes the period of convalescence. In more severe cases there may be bronchitis, phlebitis, or even nephritis, orchitis and parotitis. A peculiar loss of memory has been noted. While the usual period of the disease is three days, it may last for four or five. In fact, there are in the tropics a number of ill-defined fevers lasting from four to seven days or longer which may be varieties of dengue or sand-fly fever or both.

Mortality and Morbidity.—The disease is not primarily a serious one and the mortality is practically *nil*, but it is of considerable importance since it produces a great degree of prostration, though fortunately of a short duration. It has been a factor of great military importance, for the non-effective rate among troops who are not immune to the disease and who enter endemic zones is extremely high. It was stated that the occurrence of sand-fly fever among the British and French troops in Macedonia at one time enabled the Bulgarian forces, who were immune, to make a decided gain. Similarly, workmen and others taking up their occupations in areas where the disease exists may expect to become more or less incapacitated for a time unless preventive measures are taken.

Immunity.—Relapses following an attack of sand-fly fever have frequently been observed, but undoubtedly a lengthy immunity ultimately results which some believe lasts for life. It seems probable that hereditary immunity does not occur. Thus the majority of those coming to an endemic district from localities in which the disease is unknown are usually attacked during the first two years of their residence. It is stated by Phillips that more than 90 per cent. of such individuals are attacked. From my own experience in Macedonia, I believe this figure somewhat high. Persons living in endemic zones often claim that they are immune and may even consider this immunity hereditary but it seems far more probable that whatever immunity exists among the population of infected communities is acquired from attacks early in life.

Pathology.—This is not known as the disease is not fatal.

History.—Sand-fly was first described as a fever of three days' duration occurring in the Mediterranean basin by Pym in 1804, whose observations were confirmed twelve years later by Burnett. Since that time, there have been numerous references concerning the incidence of the disease among troops from the north of Europe serving in tropical and semi-tropical countries. In 1903, McCarrison definitely differentiated the disease in Chitral when he suspected the sand-fly as the causal agent. In 1901, Doerr, Franz and Taussig published their account of the disease mentioned above. In 1915, Castellani showed that the so-called Skoplje fever of Serbia and Macedonia is really sand-fly fever. The most recent work on the etiology of the disease was done by the Sand-fly Fever Commission of the Royal Air Force. Though the disease occurs extensively in the southern part of the United States, there has been but little written about it in this country.

BIBLIOGRAPHY

ADELMANN, E. Beitrag zur Kenntnis des Papatacifiebers. Arch. f. Schiffs. u. Tropen- Hyg., Leipzig, 1919, xiii, 81–99.

ARAVANDINOS, A. Klinische Erwägungen über das Dreitagefieber und die Dengue in Griechenland. Arch. f. Schiffs-u. Tropen-Hyg., Leipzig, 1913, xvii, 109–120.

ASHBURN AND CRAIG. Philippine Jour. of Science, Manila, 1907, II, p. 71.

BALFOUR. Sup. Third Rep. Wellcome Research Lab., 1908, p. 38.

——— Wellcome Trop. Res. Lab. Rep., 1911, iv, 219.

BASSETT-SMITH. Journal of State Medicine, London, 1897, V, p. 481.

BAUER. Bull. Soc. de Med. Mil. franç, Paris, 1924, xviii, p. 314.

BERNATSKI, A. Febris pappataci. Med. pribav. k. morsk, sborniku, St. Petersburg, 1910, Part II, p. 214.

BEVERIDGE. Journal of Royal Army Medical Corps, London, 1904, III, p. 333.

BIRT, C. O. Phlebotomus or sandfly. Brit. Med. Jr., London, 1910, ii, 875–78.

BIRT, C. Phlebotomus fever in Malta and Crete. Jr. Roy. Army Med. Corps, London, 1910, XIV, 236–268.

——— Sand-fly fever in India. 4°, London, 1910. Also Jr. Roy. Army Med. Corps, London, 1910, XV, 140–47.

——— Phlebotomus fever and dengue. Tr. Soc. Trop. Med. & Hyg., London, 1912–13, VI, 243–62.

——— Phlebotomus fever and dengue. Jr. Roy. Army Med. Corps, London, 1913, XXI, 289–401.

——— Phlebotomus fever and dengue. Brit. Med. Jr., London, 1913, II, 1297.

——— Phlebotomus or sand-fly fever. Brit. Med. Jr., London, 1915, II, 168.

BLANCHARD, R. Quelques mots sur les Phlebotomus. Arch. de Parasitol., Paris, 1908–9, XIII, 303–10.

Blau, P. Ueber Pappataccifieber. Wien. klin. Wchnschr., 1918, xxxi, 89.

Bolt, R. A. Sandflies (Phlebotomus) in China and their relation to disease. China Med. Jr., Shanghai, 1915, xxix, 78–86, 4 pl.

Boyd, J. E. M. Notes on the sandfly group and some observations on the sandfly fever at Hinaidi Cantonments, 'Iraq. Jr. Roy. Army Med. Corps, London, 1923, XL, 350–359.

Brack. Pappatacimücken und Pappatacierkrankungen. Arch. f. Schiffs-u. Tropen-Hyg., Leipzig, 1917, XXI, 381–98.

Buckridge, G. L. Some observations on an epidemic of sand-fly fever occurring in one of H. M. ships. Jr. Roy. Nav. Med. Serv., London, 1918, IV, 310–12.

Cameron, R. D. Notes on sandfly fever. Jr. Roy. Army Med. Corps, London, 1923, XLI, 369–71.

Cardamatis, J. P. Les premiers cas de fievre des pappataci observes chez nous. Atti d. Soc. p. g. studi d. malaria, Roma, xiii, 1912.

Carpenter and Sutton. Jour. Amer. Med. Assoc., Chicago, XLIV, p. 215, 1905.

Castellani, A. Tropical diseases in the Balkans. Jr. Trop. Med., London, Aug. 15, 1917.

Castro, A. Sulla febbre die tre giorni a milazzo. Malaria, Roma, 1913, IV, 68–73.

Chaplin. Lancet, London, 1864, II, p. 236.

Coquillett. Entomol. News, 1907, xviii, 102.

De Gaetani Giunta, G. Febbre dei tre giorni in Catania. Gazz. d. osp., Milano, 1911, XXXII, 1099.

Delanos, P. Existence de Phlebotomus papatasii Scopoli à Mazagan. Bull. Soc. path. exot., Paris, 1916, IX, 762.

Delmege, J. A., and Staddon, C. S. Clinical notes on Phlebotomus fever. Brit. Med. Jour., London, 1918, I, 396.

De Napoli, F. Sulle febbri estive o dei tre giorni dominanti in Bologna. Gior. di med. mil., Roma, 1911, LIX, 81–106.

Doerr. Berlin. klin. Wchnschr., 1908, XLV, 1847–49.

Doerr, R., Franz, K. and Taussig, S. Das Pappatacifieber, ein epidemisches Drei-Tage-Fieber im adriatischen Kustengebiete Oesterreich-Ungerns. Wien. klin. Wchnschr., 1909, XXII, 609.

Doerr, R., Russ, V. K. Wietere Untersuchungen über das Pappatacifieber. Arch. f. Schiffs-u. Tropen-Hyg., Leipzig, 1909, xiii, 693–706.

Dopter, C. La fièvre de trois jours. ou fièvre à pappatacis. Paris médicale, 1911, 499–503.

Ercolani, A. Appunti clinici sopra le epidemie di febbre dei tre giorni verificatesi à Forli nel trionnio, 1909–11, Malaria, Roma, 1912, III, 153–158.

Fawkes, M. The treatment of phlebotomus fever. St. Barth. Hosp. Jr., London, 1919–1920, XXVII, 23.

Foley and Leduc. Bull. Soc. path. exot., Paris, 1912, V, 511.

Franca, C. Phlebotomus papatasii Scopoli: et fièvre à pappataci au Portugal. Bull. Soc. path. exot., Paris, 1913, VI, 123.

Francaviglia, M. C. Primo caso di "febbre da pappataci" in Catania a nella Sicilia orientale. Policlinico, Rome, 1912, XIX, sez., Med., 132–140.

Franz, K. Ohorecce pappataci nebo phlebotomove, On pappataci fever. Casop. lek. cesk., v. Praze, 1914, LIII, 1059–61, 1 pl.

Franz, K., and Kolar, H. Zur Pathologie und Therapie des Pappatacifiebers. Beihefte z. Arch. f. Schiffs-u. Trop. Hyg., Leipzig, 1910, XIV, 2 Beihft., 1–26.

——— Arch. f. Schiffs-u. Trop. Hyg., Leipzig, 1910, XIV, Beiheft 2, 41–62.

PRACTICE OF MEDICINE—TICE
Insert in your Volume III these pages 649–662 immediately following Page 648.

Gabbi, U. Sul modo come avvenne la comparsa e la diffusione della febbre di tre giorni nella Sicillia Orientale e Nella Calabrin inferiore. Pathologica, Genova, 1914–15, VII, 51–55.

——— Una epidemia di "febbre dei tre giorni" a Messina e sulla costa Calabra. Malaria, etc. Roma, 1910, i, 97–100. Also: Path. Riv. quindicin, Genova, 1909–10, II, 427–29.

——— Febbre dei tre giorni o febbre da pappataci. Malaria. Roma, 1910, I, 145–50. Also Path. Riv. quindicin, Genova, 1909–10, II, 546–550.

——— Nuova epidemia a febbre dei tre giorni nella Sicilia orientale a nelle Calabria inferiore. Malaria, Roma, 1911, II, 268. Also: Path. Riv. quindicin, Genova, 1910–11, III, 449.

——— Su di una nuova epidemia di febbre dei tre giorni comparsa a Messinna e provincia. Path. Riv. quindicin, Genova, 1910–11, III, 703.

——— Studi interno alle malattie tropicali, 1912, III, No. 4.

——— Ueber den Werdegang des Auftretens und der Verbreiten des dreitagigen Fiebers in Ostsizilien sowie in Unterkalabrien. Arch. f. Schiffs-u. Trop. Hyg., Leipzig, 1915, XIX, 160–70.

——— Intorno ad una epidemia di febbre dei tre giorni. Riforma med., Napoli, 1918, XXXIV, 806–812.

——— Influenza o febbre dei tre giorni? A proposito di una recente pandemia. Riforma med., Napoli, 1918, XXIV, 572–74.

——— Febbre dei tre giorni o febbre da pappataci. Riforma med., Napoli, 1918, XXXIV, 522–24.

Gärtner, W. Epidemiologische Untersuchungen über Pappatacifieber bei der Kaiserl. Marine in der Türkei. Ztschr. f. Hyg. u. Infektionskrankh., Leipzig, 1920, xci, 262–305.

Galli-Valerio, B., and Rochaz de Jongh, J. Beobachtungen über Culiciden und Mitteilung über Vorkommen von Phlebotomus papatasi Scop. im Kanton Waddt (Schweiz). Centralbl. f. Bakteriol., 1, Abt. Jena, 1912, lxiii, Orig. 222–227.

Glasfeld, I. Iz viedemosti o bolnikh na kanonerskoi lookie "Khivinets" za iyun miesyats 1909, g. [Diseases on the torpedo boat "Khivinets" for June, 1909, Pappataci.] Med. pribav. k. morsk sborniku, St. Petersburg, 1910, 120–22.

Gonzalez, del Valle, J. G. Una enfermedad nueva. Rev. de med. y. cirug. pract., Madrid, 1911, XCI, 440–43.

Graham. Jour. Trop. Med., London, 1903, Vol. VI, p. 209.

Graham, G. F. Sandfly fever in Chitral (N. India). Brit. Med. Jr., London, 1915, II, 169.

Grassi. Mem. d. Soc. ital. d. sçienze, 1907, 3s., XIV, 353–94.

Hale, C. H. Pappataci fever at Kamptee, C. P. Jr. Roy. Army Med. Corps, London, 1912, XVIII, 505–12.

Harnett. Ind. med. Gaz., Calcutta, 1913, XLVIII, p. 45.

Hartley, J. A. Notes on an outbreak of phlebotomus fever. Jr. Roy. Army Med. Corps, London, 1918, XXXI, 317.

——— An outbreak of phlebotomus fever. Jr. Roy. Army Med. Corps, London, 1918, i, 395.

Higgins, J. T. D. S. Note on cases of phlebotomus fever at an island in the eastern Mediterranean. Brit. Med. Jr., London, 1916, I, 166. Also: Jr. Roy. Nav. Med. Serv., London, 1924, X, 31–34.

Houston, J. W. Sandfly fever in Peshawur. Brit. Med. Jr., London, 1915, II, 170–72.

Johnston, J. E., and Myles, T. W. Some observations on phlebotomus fever. Jr. Roy. Nav. Med. Serv., London, 1917, III, 326.

Joly, P. Courbature febrile epidemique de trois jours, observee a bord du nattre-hopital, "Bien Hoa." Bull. Acad. de méd., Paris, 1918, n. s., LXXX, 138–141.

Joly and Baril. Note sur une épidemie de courbature fébrile de trois jours, observée à bord du navire-hôpital "Bein Hoa." Arch. de méd. et pharm. nav., Paris, 1918, cvi, 290–308.

Jouin. De la pression artérielle (mx et Mn) de la puissance cardiaque (P) et du pouls dans le cours de la fièvre de 3 jours à phlebotome. Compt. rend. Soc. de biol., Paris, 1918, lxxxi, 719.

Kilroy and Adshead. Statistical report of the Health of the Navy, London, 1910, p. 171.

Lambert, J. Phlebotomus fever in Lemnos. Jr. Roy. Nav. Health Serv., London, 1919, LV, 144–157.

——— Phlebotomus fever. Jr. Roy. Nav. Med. Serv., London, 1923, ix, 289–297.

Langeron, M. Localités nouvelles de phlebotomes. Compt. rend. Soc. de biol., Paris, 1912, lxxii, 973.

Leger, M., and Seguinaud, J. Fièvre de pappataci en Corse. Bull. Soc. path. exot., Paris, 1912, v, 710–13.

Lehmann, K. B. Ueber Phlebotomus und Papatacifieber. Sitzungsb. d. phys.-med. Gesellsch. zu Würzb., 1914, 12–14.

Leon, Cant. F. Centralbl. f. Bakt., Jena, 1910, Orig., LIV, 521.

Lloyd, I. H. Nervous sequelæ of phlebotomus fever. Jr. Trop. Med., London, 1923, XXVI, 110.

Loughman, W. F. M. Phlebotomus fever and papataci flies in Aden. Jr. Roy. Army Med. Corps, London, 1913, XXI, 402–5.

De Luca, M. Sulla febbre dei tre giorni a Parghelia (Catanzaro) Malaria, Roma, 1914, v, 23–25.

Lutz and Neiva. Memorias do Inst. Oswaldo Cruz, 1912, Rio de Janiero, iv, 84.

McCarrison, R. The three days' fever of Chitral: a contribution to the study of the unclassed fevers of India. Indian Med. Gaz., Calcutta, 1906, xli, 7–14, 3ch.

——— A critical analysis of the etiology and symptomatology of the three-day fever of Chitral and an analogy between this condition and dengue fever. Indian Med. Gaz., Calcutta, 1908, xliii, 5–12, 3ch.

McGibbon. Jour. Can. Med. Assoc., Montreal, June, 1911.

Manteufel. Arch. F. Schiffs-u. Trop. Hyg., Leipzig, 1912, xvi, 619.

Marett, P. J. Preliminary report on the investigation into the breeding place of the sandfly in Malta. Jr. Roy. Army Med. Corps, London, 1910, xv, 286–291.

——— The life history of the phlebotomus. Ibid., 1911, xvii, 13–29, 1 pl.

——— The phlebotomus flies of the Maltese Islands. Ibid., 1913, XX, 162–171.

Martells, C. La febbre dei tre giorni a Napoli. Riforma med. Napoli, 1915, XXXI, 1156.

Melchiorre, N., and Aldo, T. Richerche sperimentali sulla etiologia della febbre estiva. Policlinico, Roma, 1910, XVII, sez. prat. 1059–1061.

Micheli, F., and Satta, G. Sulla febbre dei 3 giorni o da pappataci. Atti. d. Acad. med.-fiz. fiorent, Firenze, 1918, 187.

Miorcec, Morlaix and La Planche. La Fièvre "de trois jours." Soc. de méd., mil. franç. Bull., Paris, 1911, v, 128–134.

Miorcec and La Planche. Ibid., p. 2.

PRACTICE OF MEDICINE—TICE
Insert in your Volume III these pages 649–662 immediately following Page 648.

Mollow, W. Ueber das Pappatacifieber. Beitr. z. Klin. d. Infektionskr., Würzburg, 1919, vii, 219–236.

——— Zweiter Beitrag zur Klinik. des Papatacifiebers. Beitr. z. Klin. d. Infektionskr., Würzburg, 1919–20, VIII, 336–342.

Montefusco, A. La febbre dei tre giorni a Napoli. Riforma med., Napoli, 1916, XXXII, 120–122.

Morelli, G. Osservazioni cliniche ed epidemiologiche sopra l'attuale epidemia detta febbre da pappataci o influenza estiva. Policlinico, Roma, 1918, xxv, sez. prat. 926–31.

Morris, L. M. Phlebotomus fever in the Eastern Mediterranean during the war with special reference to its prevention. Jr. Roy. Nav. Med. Serv., London, 1923, IX, 286–89.

Muhlens. Deutsche. med. Wochenschr., 1912, xxxviii, p. 2036.

Newstead, R. The Papataci flies (Phlebotomus) of the Maltese Islands. J. Roy. Army Med. Corps, London, 1912, xviii, 613: xix, 28–162, 3 pl.

——— The papataci flies (phlebotomus) of the Maltese Islands. Bull. Entomol. Research, London, 1911–12, II, 47–78, 3 pl.

——— Ibid., 1912, Vol. III, p. 361.

Newstead, R., and Sinton, J. A. On a collection of Pappataci flies (phlebotomus) from India. Ann. Trop. M. & Parasitol., Liverpool, 1921–22, XV, 102–6.

Niclot. A propos de la fièvre a pappataci. Bull. Soc. path. exot., Paris, 1912, 780.

Owl, Midge. The Mediterranean three-day fever. Brit. Med. Jr., London, 1909, II, 100.

Pelligrino, P. L. Su la febbre da pappataci dei tre giorni; definizione, etiologia, pathogenesi, profilassi. Malaria, Roma, 1915, VI, 143–55.

Pereiva dos Santos, L. Contribucao para o estudo da "febre de papatasii" em Portugal. Med. contemp., Lisbon, 1913, xxxi, 20–23.

Phillips, L. Sandfly fever (Phlebotomus fever or "Pappatacifieber" in Cairo), Brit. Med. Jr., London, 1910, ii, 963. Also Abstract: Jr. Trop. Med., London, 1910, xiii, 246.

Pievnitski, A. A. Likhorodka "Pappatacci" (Novaya raznovidnost parazitarnikh likhoradok yuga) (Papatacci fever; a new variety of parasitic fever of the South) Voyenno med. Jr., St. Petersburg, 1909, cxxvi, med. spec. pt. 429–433.

Pires de Lima, A., Ramalhao, C., and Franca, C. Epidemia reinante e a febre papataci. Dados laboratoriais sobre a epidemia reinante. Phlebotomus portugueses. Med. mod., Porto, 1918. Also, Reprint.

Pressat. Cited by Tiraboschi and Blanchard in "Le Paludisme et les Moustiques," Paris, 1905.

Ragazzi, C. Febbre de papataci in Bengasi. Malaria, Roma, 1916, vii, 90–96.

Randone, F. La comparsa di un focolaio di febbre dei tre giorni. Malaria, Roma, 1915, vi, 247–49.

Robinson, S. C. B., and Blackham, R. J. Sand-flies and sand-fly fever on the northwest frontier of India. Jr. Roy. Army Med. Corps, London, 1912, xix, 447–452.

Roubbaud. Bull. Soc. path. exot., Paris, 1913, VI, p. 126.

Ruas, V. K. O. Das Pappataci, oder phlebotomusfieber (Doerr). Oesterr. San.-Wes., Wien., 1912, xxiv, 201–16.

Sampietro, G. L'attuale epidemia di "Febbre dei tre giorni." Ann. d'ig., Roma, 1918, xxviii, 300–14.

Sandwith, F. M. A lecture on Phlebotomus fever. Clin. Jr., London, 1911–12, xxxix, 139–143.

Sandwith. Lancet, London, 1888, vol. II, pp. 107–143.

Sarlo-Bisogni, F. Di un'epidemia di "Febbre dei tre giorni" a Francica (Provinci di Catanzaro). Malaria, Roma, 1913, iv, 82–84.

Sarrailhe, A., Armand-Delille, P., and Richet, Fils, C. Epidémie de fièvre de trois jours (dengue d'Orient) observée aux Dardanelles sur les troupes du corps expeditionnaire d'Orient. Rev. d'hyg., Paris, 1915, xxxvii, 1007–10.

——— Note sur l'épidémie de fièvre de trois jours (dengue d'Orient) observée aux Dardanelles sur les troupes du Corps expeditionnaire d'Orient. Bull. Acad. de med., Paris, 1915, 3 s., lxxiv, 317–22.

Seidelin, H. Pappataci fever. Yellow Fever Bur. Bull., Liverpool, 1912, ii, 74–84.

Shattuck, G. C. Diagnosis of "three-day fever." Tr. Am. Soc. Trop. Med., New Orleans, 1916, x, 166–72.

——— Diagnosis of "three days" fever. New Orleans Med. & Surg. Jr., 1916–17, lxix, 559.

Shreders. Lietney gripp v Sevatopolie (Febris Papatasii) (Summer grippe in Sebastopol) "Papataci fever." Morsk. Vrach. St. Petersburg, 1913, 491–94.

Signer, M. Complicanza di nefrite acuta in un caso di febbre da pappataci. Lavori d. Cong. di med. int. 1910, Roma, 1911, xx, 466. Also: Malaria, Roma, 1911, ii, 73.

Spagnolio, G. Sulla epidemia di febbre dei tre giorni osservata a Messina nell'estate, 1913 (quarta). Malaria, etc., Roma, 1914, v, 125–127.

Stitt. Bull. Johns Hopkins Hosp., Baltimore, 1913, XXIV, 117–121.

Stocker, C. J. Sandfly fever and bacteriology; vaccine treatment. Brit. Med. Jr., London, 1915, ii, 503.

Taussig. Wien. klin. Wchnschr., 1905, xviii, pp. 129–63.

Taylor, E. C., and Kahn, M. H. The diagnosis of sand-fly fever and its differentiation from malaria. Indian Med. Gaz., Calcutta, 1912, xlvii, 475.

Taylor, C. R. Sand-fly fever in Mesopotamia. Brit. Med. Jr., London, 1920, i, 620.

Tedeschi, A., and Napolitani, M. Experimentalle Untersuchungen über die Aetiologie des Sommerfiebers. Centralbl. f. Bakteriol., 1. Abt, Jena, 1911, lxi, Orig. 502.

Theobald. Rept. Sleeping Sickness Com., London, 1903, iii, p. 39.

Tonin, R. Febbre de pappataci. Gazz. d. osp., Milano, 1919, xl, 635.

Ubaldi, A. La febbre da pappataci nelle Marche. Gaz. Med. de Marche, Ancona, 1910, no. 4, xviii, 1.

Vigano, L. La febbre dei pappataci, o febbre dei tre giorni. Biochem. et. therap. sper., Milano, 1911–12, ii, 179.

Villegas, Ruis. Gac. med. de Caracas, 1924, xxxi, p. 266.

Visentini, A. Ancora intorno alle cosi delle febbre estivo a carattero epidemico (febbre dei tre giorni). Malaria, Roma, 1910, 166–69.

Wakeling, T. G. On fever caused by the bite of the sandfly (Phlebotomus papatasii). Brit. Med. Jr., London, 1910, II, 1115.

Walker, W. O. A note on the influence of atmospheric temperature on sandfly fever. Indian Med. Gaz., Calcutta, 1915, L, 60, 1 chart.

Wall, F. Sandfly fever in Chitral. Indian Med. Gaz., Calcutta, 1911, xlvi, 41–44, 1 ch.

Weinberg, M. Pappatacifieber und influenza. Arch. f. Schiffs-u. Trop. Hyg., Leipzig, 1919, xxiii, 331–37.

PRACTICE OF MEDICINE—TICE
Insert in your Volume III these pages 649–662 immediately following Page 648.

WHITTINGHAM, H. E. Observations on sandfly fever in Malta. Proc. Roy. Soc. Med., London, 1922–23, xvi, Sec. War, 1–14.

——— Phlebotomus fever. Jr. Trop. Med., London, 1923, xxvi, 11.

WHITTINGHAM, H. E., AND ROCK, A. F. The prevention of Phlebotomus fever. Tr. Roy. Soc. Trop. Med. & Hyg., London, 1924, xvii, No. 5, 290–330, 1 ch., 8 pl.

WIMBERLEY. Ind. Med. Gaz., Calcutta, 1910, xlv, pp. 281–518.

ZANNINI, W. Sopra un'epidemia della cosi detta febbre dei tre giorni in commune di Leno (Brescia). Gaz. d. osp., Milano, 1914, xxxv, 2087.

ZLOCISTI, T. Erfahrungen aus einer Papatacifieberepidemie. Berl. klin. Wchnschr., 1917, liv, 335–38.

Febbre de pappataci. Gazz. d. osp., Milano, 1917, xxxviii, 641–8.

Febbre dei tre giornio febbre de pappataci. Incurabili. Na cli, 1918, xxxiii, 121–7.